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BRAIN

A JOURNAL OF NEUROLOGY

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Brain

A Journal of Neurology

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BRAIN.

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THE CEREBELLUM OF MAN.[1]

BY GORDON HOLMES.

THE unique place that Hughlings Jackson occupies in the history of neurology depends not on descriptions of diseases or syndromes previously unrecognized, but on the methods which he introduced into the clinical study of the nervous system and on the numerous contributions he made to the modes of its activity in health and in disease. He insisted upon accurate observation, on a careful and systematic analysis of the facts observed into their simplest components, and a study of the latter for the light they may throw on the normal functions of the organ which is affected. As the cerebellum repeatedly claimed Jackson's interest a study of its functions by the methods he taught is an appropriate subject for a lecture devoted to his memory.

My aim in this study will be to review facts or observations which have been acquired since my previous contributions to the symptomatology of cerebellar lesions (Holmes 1917-1922), to reinterpret where necessary earlier observations, and to discuss their physiological significance. During these sixteen years numerous clinical observations have been published and an enormous amount of experimental work has been devoted to the cerebellum, but the conclusions drawn from them are so discordant that it seems wiser to omit reference to them when possible and to attempt an independent study of the symptoms which result from lesions of it in man, describing them as simply and unequivocally as possible without the use of the conventional terms which have undoubtedly confused the subject.

The divergencies between the observations of those who have studied experimental animals is particularly confusing; for instance, numerous physiologists as Rademaker, Dusser de Barenne and others have failed to find many of the symptoms with which the clinician is familiar, and even within the last year Keller, Roy and Chase have concluded that in dogs, and even in monkeys, the neocerebellum, which includes the greater part of the organ in man, is not essential for any of the functions which have been attributed to it. Other physiologists, however, as Bremer and Fulton and his collaborators, have recently described disorders similar to those which the clinician sees. The discrepancies are largely owing to the animals used in the experiments, for in the carnivora removal of the cerebellum causes few characteristic disorders, and even in the monkeys the symptoms are not pronounced and often transient; it is only in the apes that, to use Fulton's words, "conspicuous and enduring" symptoms occur. It is therefore obvious that the activity of the cerebellum is more essential in the higher steps of the phylogenetic ladder, and a physiological study in man may consequently provide more valuable information on its functions. Further, as Walshe (1927) and others have emphasized, the disorders which result from destructive lesions are seen mainly in voluntary movements, a greater range and variety of which can be investigated in man than in lower animals.

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[1] The tenth Hughlings Jackson Memorial Lecture delivered before the Section of Neurology, Royal Society of Medicine, on December 16, 1938.

HYPOTONIA.

Diminution of muscular tone is now generally recognized as one of the fundamental symptoms of acute cerebellar injuries in man, but it is less apparent or less easy to detect in chronic or long standing disease and in some of the systemic degenerations. It has been denied that hypotonia occurs in lower animals after extirpation of the cerebellum, but Bremer has recognized it in the cat and dog, and Fulton and Dow described it as "conspicuous and enduring" after even small lesions of the neocerebellar cortex in apes.

A clear definition of what is in this connection meant by tone is essential as the term has been often applied by physiologists and clinicians to different states of muscle. To the clinician tone generally means the constant slight tension characteristic of healthy muscle, which offers a steadily maintained resistance to stretching; it is recognized by the resistance experienced when the limbs are moved or displaced passively. Sherrington describes tone as a steady contraction of muscles dependent on the activity of spinal reflexes but modifiable by supra-segmental mechanisms, the function of which is maintenance of posture and postural adaptation. Owing to its plasticity the tension of normal muscle is immediately adjusted to changing conditions and remains constant regardless of its length. It is in this sense the term is employed here. A lack of tone can often be recognized by handling the limb, but the essential fact is that the hypotonic limb can be displaced with unnatural ease from any position determined by contraction of its muscles ; its posture is not adequately fixed by their tonic contractions.

The presence of hypotonia in cerebellar disease can be demonstrated by many clinical tests, but as confusion still exists as to what is denoted by the term in modern neurology a few instances may be given. If, for instance, the outstretched arms rest lightly on a bar the normal limb keeps its position or sags but little when the bar is suddenly removed, but the hypotonic arm falls through a greater angle and may fail to maintain its new posture (fig. 1). This is more striking if the hand carries even a moderate weight ; when its support is released it falls more abruptly, sways about and regains stability slowly, and irregular contractions can be seen or felt in the muscles that should hold it up (fig. 2). The leg in like manner falls heavily and inertly to the bed when it is suddenly unsupported. When the arms are extended horizontally the affected limb is more easily displaced by a tap on the wrist ; it gives at the shoulder and frequently flexes or extends passively at the elbow. When shaken the distal segments of the limbs swing more passively and through a greater range. Similarly, if while the

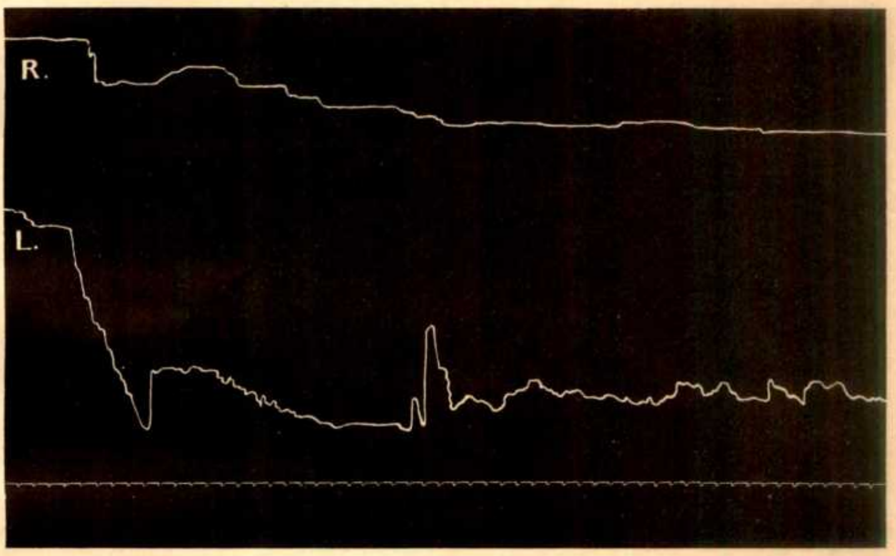

FIG. 1.—A support was suddenly withdrawn from the two outstretched arms of a man with a lesion of the left side of the cerebellum. The left (affected) arm fell at once through a larger angle and developed an irregular tremor. The time marker records seconds.

patient stands erect he is rotated or otherwise moved the hypotonic arm swings more freely. If while a normal person is lying supine a leg is suddenly jerked upwards by a hand under the thigh, the heel rises from the bed since the tone of the quadriceps extensor tends to keep the knee extended, but in the hypotonic limb the knee flexes at once and the heel merely drags along the bed or floor.

It is true that the patient may succeed for a time in maintaining a posture by contracting voluntarily the muscles acting on the joint or joints concerned, but the limb soon becomes tremulous and the effort tires; on the other hand a limb in which posture depends mainly on tone is relatively indefatigable.

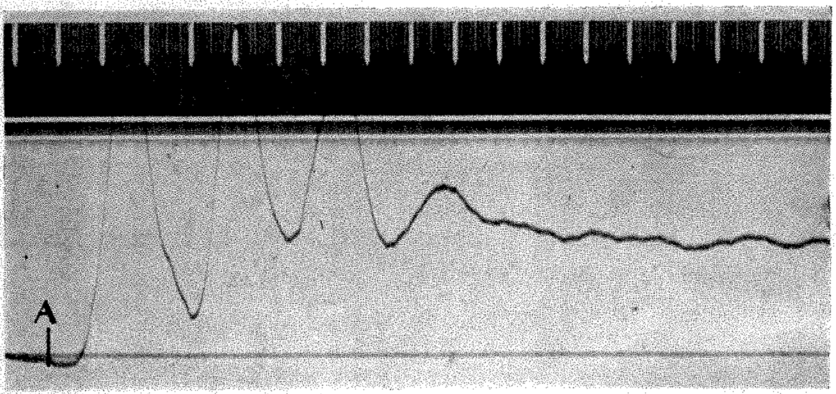

FIG. 2.—A tracing obtained by a tambour placed over the biceps muscle. The hand carried a weight of 2 pounds; at A a support on which it rested was suddenly removed. The tracing shows the irregular contractions of the muscle when it was exposed to the sudden strain, and its delay in acquiring even relative stability. Time in 1/5 seconds.

These examples illustrate the effects of diminished postural tone which alone, or by reinforcing voluntary effort, tends to fix each part of the body in the attitude which it occupies, and they show that volitional contraction of the muscles alone is not adequate to maintain posture.

But tone plays an equally important part in movement, which can be regarded in Jackson's words as a succession of postures; it co-operates with the phasic contractions of the muscles and by virtue of its plasticity assures the appropriate attitudes of the moving segments, as well as the postures of the parts on which they move. It may be that in long-standing disease of the cerebellum and in such slowly progressive affections as the systemic degenerations, the muscles regain through the activity of other parts of the nervous system some capacity to fix attitudes and to resist stretch so that hypotonia is not so easily recognized on clinical examination, but the more complex function of adapting tone to changing posture during movement remains defective and contributes to the disturbances included in the term "ataxia."

When one side of the cerebellum alone is injured the hypotonia, like the other motor disorders, is restricted to the muscles of the same side of the body, and it appears that no matter how small the lesion may be all the muscles of this side are hypotonic. It is usually more easily demonstrated in the arm than in the leg, and is more pronounced in the proximal muscles which are normally more concerned in the determination of postures.

The fact that the knee-jerk and other stretch reflexes can be elicited has been an argument against the existence of hypotonia (Sager), but though the cerebellum may augment muscular tone the absence of this function does not abolish the spinal reflexes. In the presence of an acute cerebellar lesion the stretch reflexes may, however, be modified. Frequently the knee-jerk is not so easily obtained, or the response to a tap on the patellar tendon may be variable, or the excursion of the leg may be excessive. The character of the jerk may be altered too, since owing to the absence of a "shortening reaction," or tonic contraction supervening on the initial contraction of the quadriceps, the momentum of the falling leg is unchecked and it swings like a pendulum, as it would if it were merely hinged at the knee (fig. 3). Sherrington (1915) has in fact emphasized that the knee-jerk is not a postural reaction and is therefore not a direct sign of tone, but the "shortening reaction" appended to the jerk contraction is, and he has

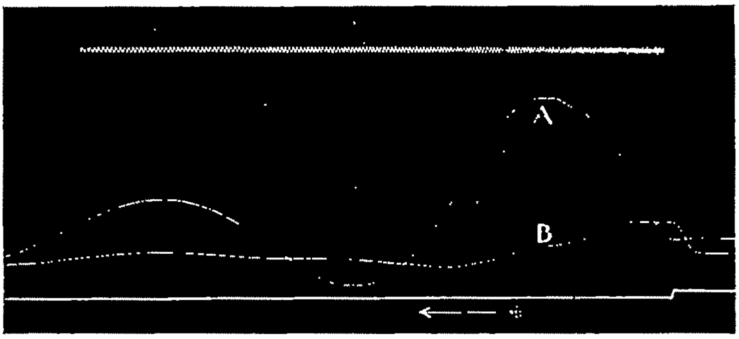

FIG. 3.—Tracings from a pendular knee-jerk. A records the displacement of the leg and its first oscillation after the jerk: B, a tracing obtained by a tambour placed on the quadriceps muscle. In the latter no after-contraction is visible. Time by a tuning fork of 128 vibrations per second. Read from right to left.

described characteristic pendular jerks in states in which the reflex excitability of postural tone was low. The pendular knee-jerk of cerebellar disease is consequently evidence of diminished postural tone. It is also an illustration of the influence which the cerebellum may exert on primitive spinal activities.

When in a limb possessing normal muscular tone the patellar tendon is struck, an immediately following contraction of the hamstrings can be readily felt by fingers placed behind the knee ; like the quadriceps, these muscles respond to the sudden increase of tension in them due to extension of the leg. This is often absent on the side of a cerebellar lesion ; in the flexors of the knee as in the extensors there is a less regular reaction to stretch, and its absence increases the tendency to passive oscillation of the leg.

There are other phenomena associated with, and probably related to, the tonelessness of the muscles and their failure to respond readily to sudden elongation. When, for instance, a normal elbow is flexed strongly against resistance and the resistance is suddenly released the excursion of the movement is quickly checked, but the toneless forearm flexes till arrested mechanically. Similarly, when the arm is relaxed the hand can be flung into the patient's face with so much force as to hurt him ; even when repeated several times the patient fails to arrest his limb, or prevents his hand striking his face only by diverting it to another direction. That this is not simply due to a failure of voluntary effort to arrest the moving hand is shown by the fact that in a spastic limb, in which voluntary control as well as the cortical reflexes are defective, the movement is checked at once, and the elbow may be extended by an abrupt contraction of its extensors in response to a sudden increase of tension in them.

Similar phenomena can be observed in the lower limbs. When relaxed the leg can be thrown to the bed, or to the floor, or against the other limb with such momentum as actually to hurt the patient.

From these observations it is obvious that the hypotonic muscles do not respond by contraction to a stretch suddenly imposed on them so readily as the normal.

The abnormal attitudes frequently observed can be also explained by the hypotonic state of the muscles. If a unilateral cerebellar lesion is present the ipsilateral shoulder often droops, the arm hangs fully extended by the side and the limbs may lie in any position to which gravity has brought them. Several observers have recognized that in man and animals attitudes which would normally cause discomfort are less promptly corrected, and some, as Lewandowsky, Goldstein and Dusser de Barenne

(1937), have interpreted this as due to sensory defects or to disturbances in the afferent paths. From numerous examinations I have no doubt, however, that in man even extensive lesions of the cerebellum involve no form of conscious sensation. In the normal limb the discomfort of an unnatural attitude is due mainly to tension in the overstretched muscles; owing to diminished elasticity of the hypotonic muscles their intrinsic receptors are not excited by the same degree of elongation.

The instability of a limb and the irregular tremor which develops in it during attempts to maintain attitudes against gravity and mechanical forces are evidently due to defective postural fixation and to voluntary corrections of its deviations. Sherrington (1915) has shown that at lower levels of the nervous system postural tone fuses with muscular contractions otherwise excited and makes them more continuous and sustained. A failure of postural tone to reinforce voluntary attitudes is obviously one of the causes of such tremor, which is consequently related to hypotonia. It is doubtful if fatigability, which is a feature of the hypotonic limbs, is an important factor, or if asthenia of the muscles plays a part, as the limb may become tremulous as soon as it is unsupported (fig. 1).

Occasionally a more regular and rhythmical tremor occurs, probably when the superior peduncles are injured; Ferrier and Turner originally described such tremor after section of these peduncles, and this has been confirmed by Walker and Botterell and by Fulton and Dow in primates.

Rigidity or a hypertonia of muscles has been described by several workers after ablation of the palæocerebellum (Rademaker, Sager), and Hughlings Jackson (1890) described tonic seizures in patients with lesion of the vermis. In man, however, the palæocerebellum is represented by a relatively small part of the organ, and it can be rarely involved alone by local lesions. I have no definite observations that muscular tone is ever increased in cerebellar disease, but I have seen a few cases of anterior and mesial lesions in which the characteristic disorders of movement were not accompanied by a definite diminution of tone.

ASTHENIA AND FATIGABILITY.

Since Luciani originally described asthenia, or paresis of movement, as one of the fundamental features of destructive lesions of the cerebellum there has been much dispute as to whether muscular power is ever affected. Most of those who have undertaken animal experiments have failed to confirm Luciani's statement, but Bremer, Rossi and Simonelli, and Fulton and Dow observed evidences of feebleness in animals soon after operation. Goldstein has described it in man, and measurements which I have published place beyond doubt that it occurs (Holmes, 1917). In acute lesions strength may be reduced to half that of the normal limb, but though asthenia may persist for months it diminishes gradually or becomes less apparent. The following figures represent the averages of several measurements obtained from two patients with gunshot wounds of one side of the cerebellum. In one the measurements were made nearly ten weeks after the wound was inflicted.

	Case 1 (thirty days).		Case 2 (sixty-eight days).	
	Unaffected Side (R)	Affected Side (L)	Unaffected Side (R)	Affected Side (L)
Grasp	12·4	5·8	17	10
Flexion of Elbow	26·2	15·3	10	7
Extension of Elbow	11·8	5·2	7	4·6
Supination	10	5·2	—	—
Pronation	20	14·5	—	—
Depression of Arm	—	—	10·4	6·5
Flexion of Ankle	—	—	12·5	10·5
Extension of Ankle	17	15	18	15
Depression of Leg	—	—	10·5	9

This feebleness is often recognized by patients; many complain that the arm particularly "feels weak and heavy," "I have to put more effort into it to move it," "I can't put force into it," "I can't lift the same weight with it." It is usually greater in the proximal segments of the limbs, and in the arm than in the leg. There is often associated with it an obvious reluctance on the part of the patient to move the affected limbs, especially in gestures and spontaneous actions. Although always greater in hypotonic limbs there is no evidence that asthenia is due to disturbance of tone, and as it can be demonstrated in even the simplest actions it cannot be attributed to defective co-operation of muscle groups or to disorders of movement. It must therefore be regarded as a primary or fundamental symptom.

A tendency of the affected limbs to tire more readily than the normal has been generally recognized; Botterell and Fulton have described it in apes. It seems to be closely related to the degree of asthenia which is present.

Disorders of Voluntary Movement.

But the most prominent disturbances of function that result from destructive lesions of the cerebellum are disorders of voluntary movement. These disorders are usually described under such terms as "ataxia," "incoordination" and "asynergia," but to avoid confusion to which they have given rise they will be employed here as little as possible.

In dealing with these disorders of movement it is important to recall

Hughlings Jackson's teaching. He insisted "It will not suffice to speak of co-ordination as a separate faculty, co-ordination is the function of the whole and of every part of the nervous system" (1870). And he repeatedly pointed out that there are two factors in the causation of irregularity of movement; "Half of the symptomatology of disorders of co-ordination with negative central lesions is paralysis (i.e. loss of function) owing to that negative central lesion. But the other half is from forcing of other movements by overactivity of perfectly healthy nervous arrangements." . . .

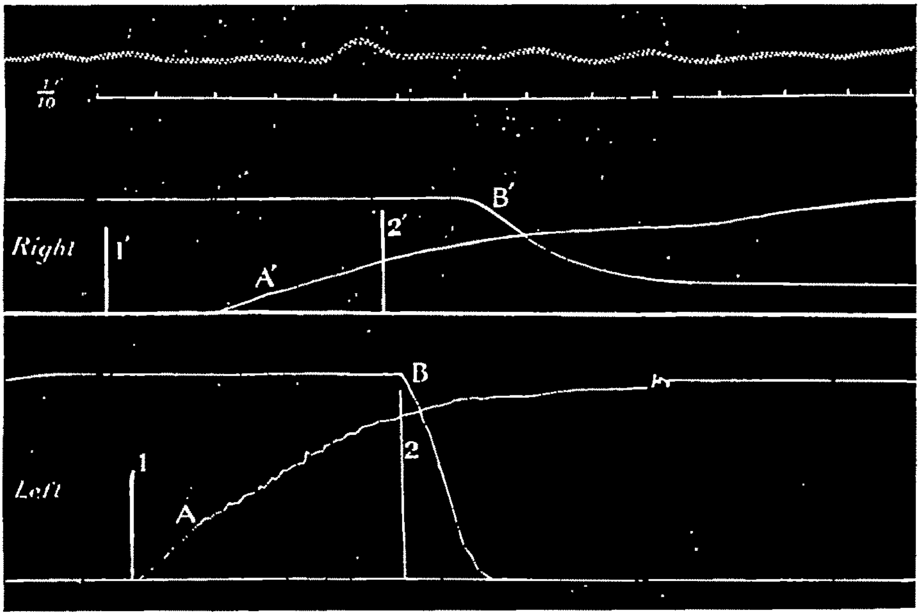

Fig. 4.—From a case of injury to the right lateral lobe. The patient was asked to grasp simultaneously with his two hands against two springs of equal strength. 1 and 1¹ represent the simultaneous ordinates, A and A¹ the lines traced on a rapidly revolving drum. The drum was allowed to complete one revolution and a signal to relax was then given; 2 and 2¹ represent the simultaneous ordinates, and B and B¹ the tracings of relaxation. Time by a tuning fork of 128 vibrations per second. (Holmes, 1917.)

"The two elements, negative and positive, constitute the disorder of co-ordination" (1888).

An attempt to resolve these disorders into their simplest factors can be most profitably undertaken by studying first simple movements, that is movements at one joint and in one direction only, the rest of the limb being fixed, as flexion or extension of a single finger, or of the elbow or knee. One of the great disadvantages which clinical investigations suffer is difficulty in recording and measuring observations accurately by such methods as physiologists employ. Tracings of simple movements can be obtained on a revolving drum, but the most satisfactory method of recording more complex movements is to attach to the moving part a small electric bulb which is made to flash at rapid but regular intervals by a tuning fork interposed in the circuit and photographing the flashes on the plates of a stereoscopic camera in a darkened room. By this means a permanent record of the rate of the movement and of its direction in all three planes of space is obtained (see fig. 7).

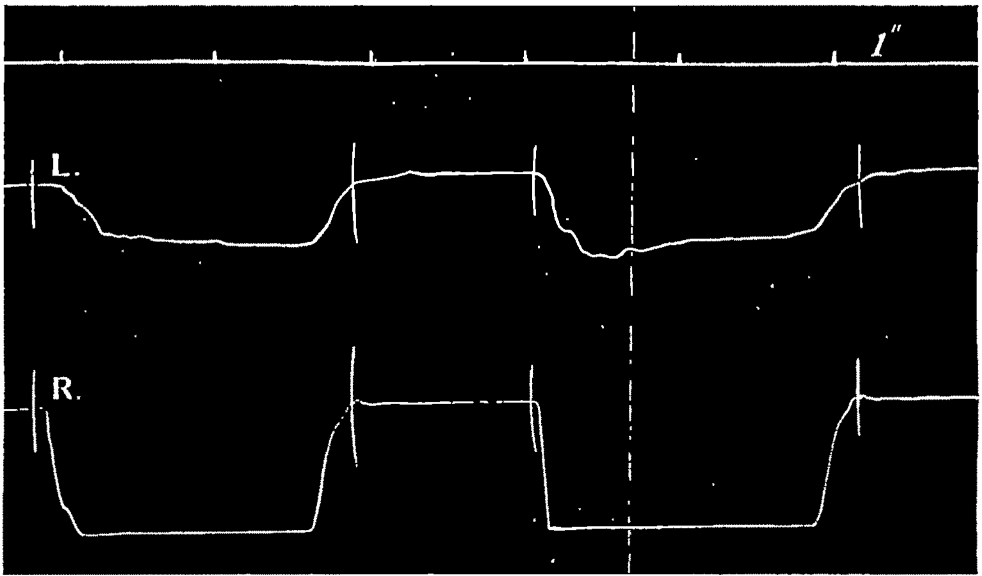

Fig. 5.—Tracings on a slowly rotating drum of simultaneous depression of the right and left arms against springs of equal tension, from a man with a lesion of the left side of the cerebellum. The tracings show delay in starting and slowness in effecting the movements, reduced and irregular exertion of power, and slowness in relaxation on the affected side. Time in seconds.

Simple movements.—If a simple movement is studied, as flexion or extension of a single finger, or of the forearm at the elbow, while the rest of the limb is supported or fixed, the most prominent abnormalities are due to disturbances in its rate. In the first place there is frequently a delay or slowness in starting motion. This is more readily seen in unilateral lesions when the patient is requested to execute the same movement with the two limbs at a given signal, as to grasp an object simultaneously with his two hands, or to flex or extend his fingers to order (fig. 4). As I have previously pointed out (1917), the slowness in initiating a movement is generally more pronounced when the patient is not immediately prepared for the signal and in the ordinary activities of the limb, but it is usually apparent even after repeated examinations and when he is aware of the purpose of the test. It occurs equally in unrestricted and in opposed movements. In cases of mild disturbance this delay in initiation may be detected only when tracings of symmetrical movements are taken on a rapidly rotating drum, but it is usually visible or can be felt by fingers placed on the moving part. Goldstein, Bremer and other clinicians have also observed this phenomenon, and Fulton and Dow have described "a conspicuous slowness in initiation of movement" in the chimpanzee. Risien Russell, in experiments on monkeys, was also impressed by the tardy withdrawal of the affected limbs from noxious stimuli. It is usually present in all movements of the limbs, but is often more pronounced at the proximal joints, that is in segments moved by the larger muscles (fig. 5).

Not only are movements initiated more slowly but they usually attain their ordinary velocity and force more tardily than in the normal limb. This is more obvious if the movement is performed against a resistance, as compressing a dynamometer or pulling against a spring. Under these conditions it may be often seen that the exertion of force is also jerky or intermittent in contrast with the rapidly and steadily increasing power developed by the normal limb (fig. 5).

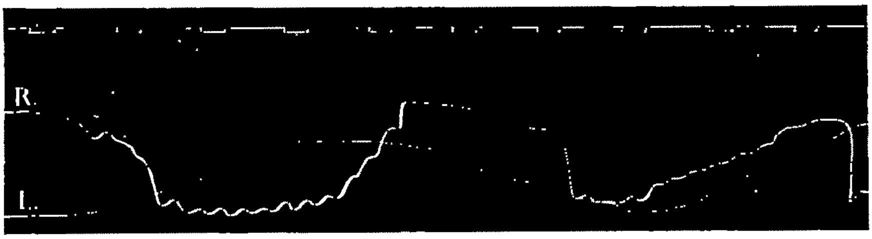

FIG. 6.—A patient with a right-sided cerebellar lesion was requested to flex and extend each index finger at a slow and uniform rate. The separate tracings were obtained on successive rotations of the drum. The jerky and tremulous character of the movements of the right finger contrasts with the regular and uniform rate of those of the left. Time in seconds

An equally important though less recognized disorder in all movements, but particularly in those executed slowly and deliberately, is a lack of uniformity in their velocity. Within even short intervals their speed varies, being sometimes slower, sometimes faster than in the normal limb; the natural rhythm and regularity of motion is lost (fig. 6). This can be

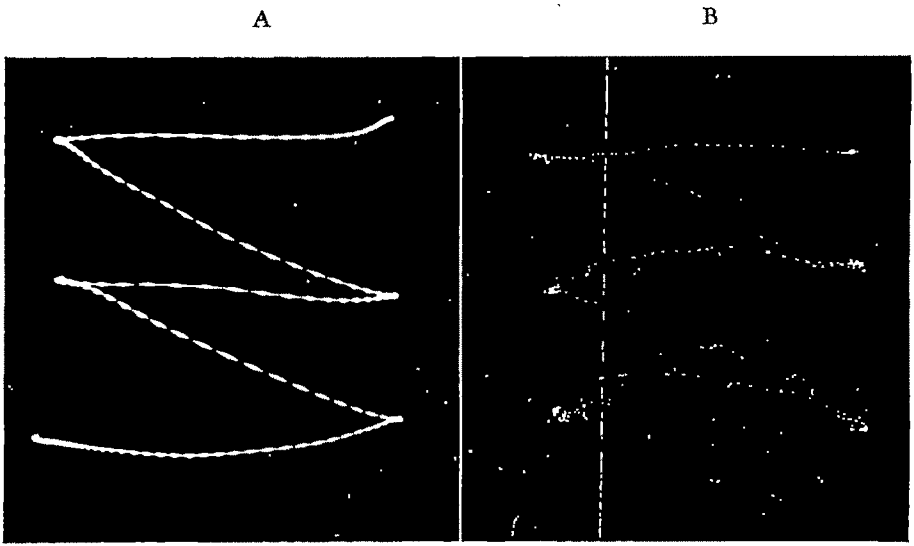

Fig. 7.—Records obtained by photographing points of light attached to the tips of the forefingers as a patient with a lesion of the right side of the cerebellum attempted to move each finger slowly and accurately between series of luminous red points (not visible in the photographs) in a dark room. Each flash of light corresponds to 0 04 second. The range of each movement was about 75 cm. A is the record obtained from the left hand, B, that from the right. The irregularity in the rate and in the directions of movements of the affected hand, and the failure to arrest this finger accurately at the points, are well shown in B.

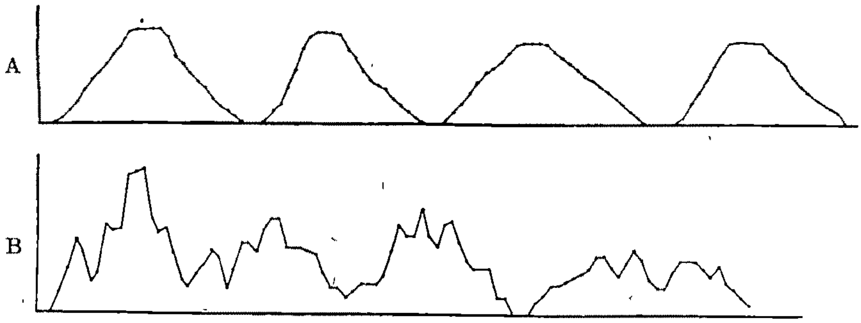

Fig. 8—An analysis of four of the separate movements of each record in fig. 7, A and B, to show irregularity in the velocity of motion of the right hand (lower curve). The horizontal distance between each dot corresponds to 0·04 second; the heights above the base lines represent the spaces between successive flashes of light and therefore the rate of movement at the corresponding points in space. In three of the excursions of the affected limb he failed to bring the finger to rest on reaching the point to be touched (lower curve).

particularly well demonstrated by analysis of light records, as when this method is employed there is no mechanical restraint to steady the movement (figs. 7 and 8), but it can be also recognized in resisted movements in which the exertion and maintenance of power is jerky and discontinuous (fig. 9). The irregular velocity of movement may appear as an obvious tremor, but the variations in rate are frequently so rapid and small that they can be recognized by graphic methods only.

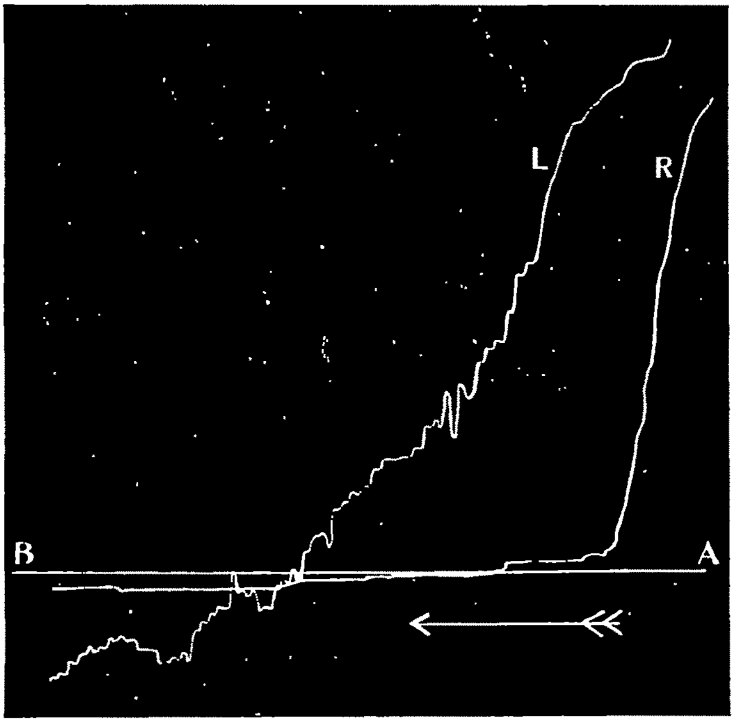

FIG. 9.—The patient, who had a wound of the left side of his cerebellum, was asked to extend springs of equal strength with his two arms on a signal and to maintain the stretch at a level indicated by the line A, B Note the slowness of the left arm in exerting power, the irregular tremulous character of the movement and the failure to maintain the final posture. Read from right to left.

When one side only of the cerebellum is injured the whole range of movement of the ipsilateral limbs in both man and apes (Fulton and Aring) is often slower and more deliberate than of the normal, but if the limbs are uncontrolled they may attain a greater speed (fig. 10B); the arm or leg may be flung out with unnatural force and velocity, and the hand may swoop down on, or snatch at, any other it wishes to reach. This is particularly seen in movements with gravity, or when a restraining force is suddenly removed.

In such simple movements there is rarely any pronounced deviation from the direct line provided the proximal segments of the limb are supported or fixed.

The most obvious errors are, however, seen towards the end of movement. As a normal limb approaches its object its velocity declines at a uniform rate till it comes to rest, but the speed of the affected limb is often unchecked till the object is reached or even passed (figs. 7 and 8), and then the error is corrected by a series of jerky secondary movements, or the finger or toe may swing around the point to be touched without actually coming to rest (fig. 10). This excessive range of movement, to which the term "hypermetria" has been applied, has attracted much attention and has been regarded as a characteristic feature of "cerebellar ataxia," but it occurs in other hypotonic states.

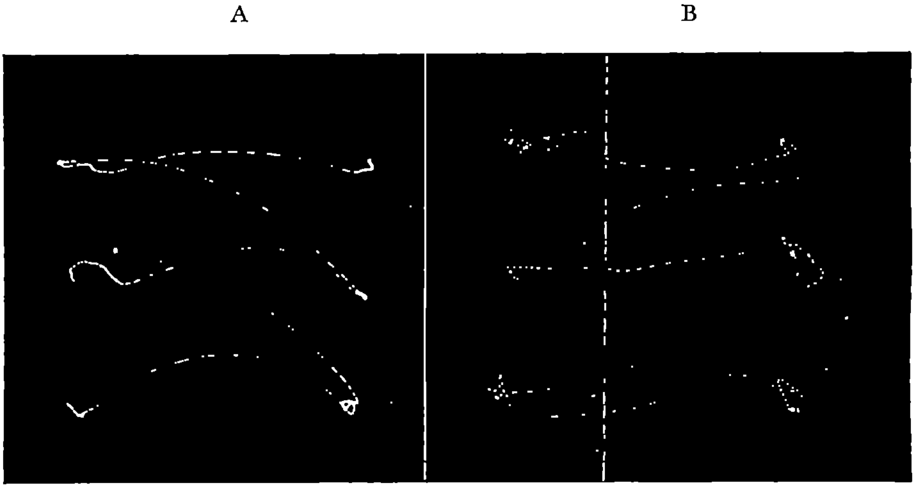

Fig. 10.—Light records as in fig. 7. A is a record obtained from a patient with a lesion of the left side of the cerebellum; B, from another patient with an injury of the right lateral lobe.

When movements against resistance are studied by graphic methods it is found that hypermetria is due to delay in starting their arrest and slowness in completing it (figs. 4 and 5). The movement, or rather the contractions of the muscles which effect it, may be continued for a fifth of a second or more after the normal limb has come to rest; a fifth of a second may represent a large part of a simple action. These abnormalities in relaxation are very similar to those at the start of movement. Sometimes the one, sometimes the other are the more prominent.

Frequently, however, the excursion of the limb is arrested too soon and the object is attained by similar correcting movements. This premature arrest is sometimes merely a manifestation of lack of uniformity in the rate of movement, but it seems to be commonly due to a voluntary check; it occurs particularly in patients who have experienced the risk of overshooting the mark.

Tremor, which is sometimes apparent during the whole range of movement, is usually more prominent towards its end; the irregular oscillations in the intended direction result from failure of uniform deceleration, but this is complicated by secondary or correcting jerks when the object has not been accurately reached in the first attempt (fig. 7B).

Delay in starting movement and slowness and irregularity in its acceleration are probably fundamental disturbances; as the latency of atonic muscle is not altered they cannot be attributed to hypotonia. The irregularity in rate and force during movement have been attributed to lack of a steadying influence or grading action of the hypotonic antagonists; this is undoubtedly an important factor in slow and deliberate acts, but as these irregularities may be equally pronounced, or even greater, in movements executed against resistance, in which the antagonists are normally relaxed (fig. 9), this explanation is not adequate. They must be therefore attributed to irregular innervation of the prime movers.

Altenburger has described a variation in the action currents of contracting muscles which he regards as a characteristic and fundamental feature of cerebellar affections. His records show, instead of a normally continuous or rhythmical series of oscillations during contraction, groups of separate oscillations, each representing 6-15 action currents, occurring at more or less regular intervals at a rate of 4 to 5 per second. Such a breaking up of the action currents, indicating a discontinuity in muscular contractions, would correspond with the unevenness in rate and force of movement which can be observed directly and demonstrated graphically, but unfortunately his published records were obtained mainly from cases with mesencephalic lesions (Bindearmläsion) and of disseminated sclerosis in which there occur coarse tremors at rest and during motion which differ in essential respects from the characteristic irregularities of movement of cerebellar ataxia. Dr. Denny-Brown, who kindly recorded the action currents in some of my patients with local lesions of the cerebellum, was unable to confirm Altenburger's findings (fig. 11). When an obvious tremor develops at the end of movement rhythmical or irregular intermissions naturally occurred in the records, but no tendency to a grouping of action currents separated by regular intervals could be observed in any stage of either free or opposed movement. Frequently, however, a waxing and waning of the intensity of the action currents could be seen when the muscles from which they were obtained were contracting irregularly (fig. 11A).

Errors in range of movement, apart from premature voluntary arrest, are simply manifestations of failure of prompt and uniform deceleration which must be due to a primary disturbance in innervation, but delay in the intervention of the antagonists to check the movement is certainly another factor. There is no evidence that hypermetria is the direct result of absence of a special "braking" function which the cerebellum exerts in movement (Babinski, Söderbergh, Schilder, Barkman).

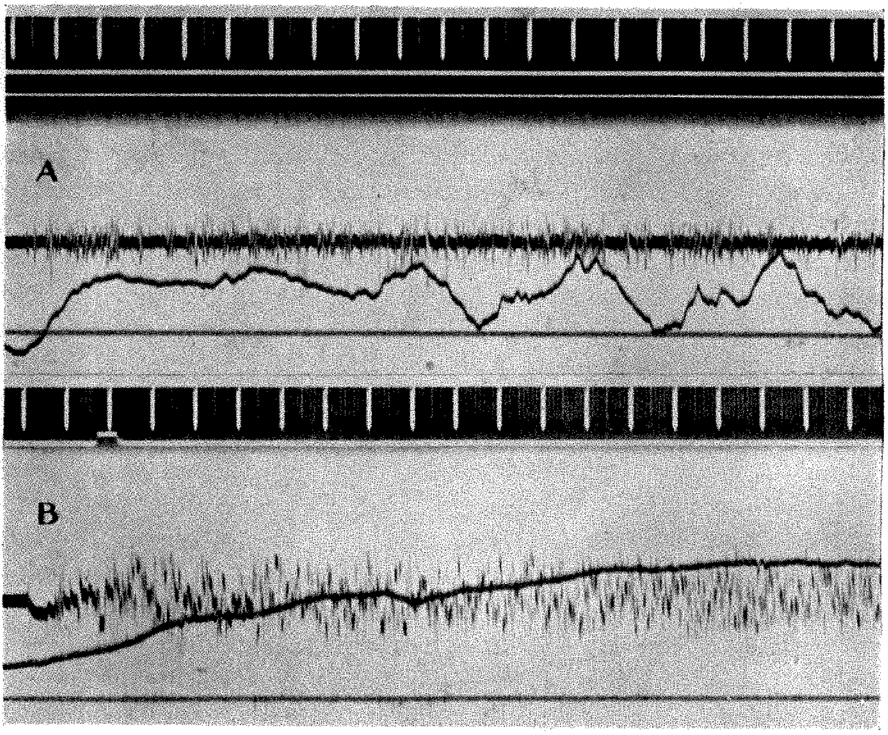

FIG. 11.—Records of action currents from two patients with pronounced cerebellar ataxia. A was obtained from the deltoid during unrestricted abduction of the arm. B obtained from the flexor carpi ulnaris during opposed flexion of the wrist. The unbroken line in each record was obtained by a tambour on the active muscle and represents its contraction.

These abnormalities of simple movements are generally most pronounced in hypotonic limbs ; their relation to hypotonia will be discussed later.

Compound movements.—This term may be applied to movements which involve change of posture at two or more joints, as bringing a finger to the nose, or a heel to the opposite knee. To facilitate description they can be divided into (1) movement in one direction, and (2) movement requiring a change in direction.

In *compound movements in one direction* the irregularities in rate, force and range of each component of the movement complicate the execution of other synchronous or successive components and therefore combine as it were in geometric progression so that the error of the whole movement is relatively greater than the sum of those of its parts.

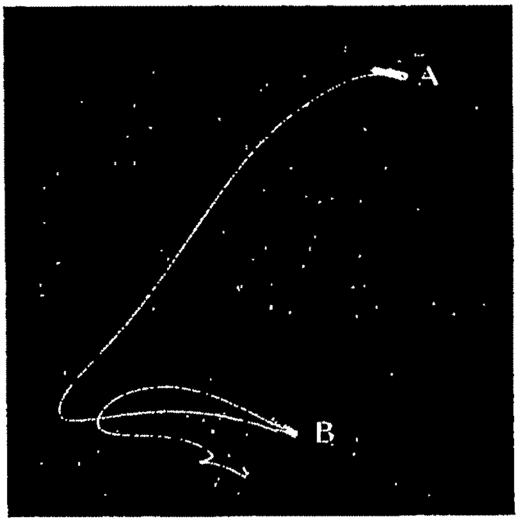

FIG. 12.—Decomposition of movement. The patient attempted to bring the tip of his finger from a point A above his head to his nose B. He executed the act in two stages ; in the first he merely depressed his arm, and in the second stage he brought his finger towards his nose by flexing his elbow. After striking his nose violently the finger was withdrawn and then brought back irregularly. The record was made on a stationary camera plate by a light attached to the tip of the moving finger.

There are, however, other factors in so-called "cerebellar ataxy." In the first place there may be a lack of synchronicity in the separate components of the movement. If, for instance, the patient with a unilateral lesion is requested, when his arm is extended above his head, to bring his index finger to his nose, with his normal limb he does so by simultaneously depressing his elbow and flexing his forearm, so that the tip of the finger follows a more or less straight line from the start to the end of the movement, but on the affected side depression of the elbow is frequently completed before the forearm flexes (fig. 12). When asked to touch a point at arms-length in front of him he often first extends his arm and then swings it about till the finger reaches its aim. Similarly in bringing a heel to the opposite knee the thigh may be bent on the trunk before the knee is adequately flexed, or the knee may flex first. The affected limb "decomposes" the movements in time into its constituent parts, and this naturally leads to errors in direction. Delay in the initiation of one component relative to that of another, and excessive range of one element of the movement, particularly at a proximal joint, are the chief causes of "decomposition," but another factor is the defective fixation of one or other of the moving joints.

Defective postural fixation of the moving limb is also largely responsible for errors in direction of movement which are often a dramatic feature of "ataxia." I have previously drawn attention to its importance (1917) and Noica has described it as the most potent factor in the disorders of movement. Its influence is generally greater at the proximal joints where the weight and momentum of the moving limb particularly require steadying by tonic contraction of the muscles around them. We have seen that when the hypotonic limb is held horizontally outstretched, subject only to the unvarying force of gravity, it soon sags or deviates from its position; such deviations are more likely to occur if posture is complicated by motion of any segment, since the force to which the fixing muscles are exposed varies rapidly with changes in the centre of gravity and in the momentum of the limb. The hypotonic muscles also seem to lack the plasticity by which they can rapidly adapt themselves to changing conditions. The result is that the moving limb is liable to sway about, especially at the shoulder and hip, instead of conforming accurately to the posture or displacement required of it in the action. Finally, lack of a steady or properly adapted base on which to move necessarily interferes with and impairs the accuracy of movement of the more distal segments of the limb.

The influence of deficient postural tone on movement extends to the distal segments of the limbs also. When a patient attempts to bring in succession each finger separately to the tip of his thumb, the thumb frequently fails to keep or to adopt correct postures, and all the fingers tend to flex simultaneously instead of individually, as those which should remain extended are not held in this position by the tone of their extensor muscles. Inability to maintain the correct postural relations of the fingers to one another, to keep those not directly concerned out of the way, is partly responsible for the difficulty in performing delicate actions, as buttoning clothes, striking notes on a keyboard and handling objects.

In movements in which there is a change in direction irregularities are more striking. They may be seen when a finger follows an object which does not keep to a straight line, and when the patient attempts to outline a square or a more complicated pattern it is at the turning points that errors are most pronounced (fig. 13); the overshooting of the aim or the premature arrest of the limb, the attempts at correction, the terminal tremor, and the delayed and irregular start of the next phase, all lead to confusion and inaccuracy. Frequently the finger merely sweeps in a curve round the turning point instead of pausing at it.

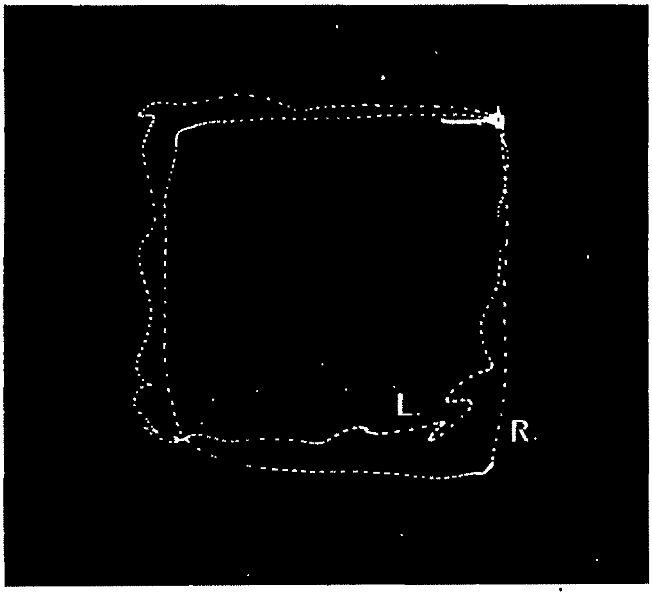

Fig. 13.—Light records of attempts by a man with a lesion of the left side of the cerebellum to outline the square end of a room with the right and left (affected) forefingers in succession. Each flash of light represents the distance covered by the moving finger in 0·04 second.

It is particularly in actions which require reversal of direction that these disturbances are prominent. Babinski, who first recognized the inability of the affected limb to execute alternating movements with normal rapidity and regularity, gave it the name dysdiadochokinesis.

The slower rate and the lack of rhythm depend mainly on time lost at the turn or in reversal; this is partly due to delay in initiating each successive movement, but tracings also show that the individual excursions are usually less rapid than when the normal limb is engaged (fig. 14) but they may attain a greater velocity (fig. 15). The factors which retard simple movements cannot, however, explain fully the slower rate; it seems probable that a defect in post-inhibitory rebound, which Sherrington (1913) has shown facilitates the transition of one movement to another in the opposite direction, is partly responsible. Since simple segmental reflexes, as the knee-jerk, may be influenced by cerebellar lesions, we may assume that other spinal activities, as post-inhibitory rebound, may suffer too. The fact that the rate, rhythm and range of alternating movements may be improved, and may even approximate to the normal, when the patient carries a heavy bar in his hand during the pronation-supination test, points to its importance, for the increased momentum of the moving limb increases the tension on the antagonists and excites more readily their succeeding contraction.

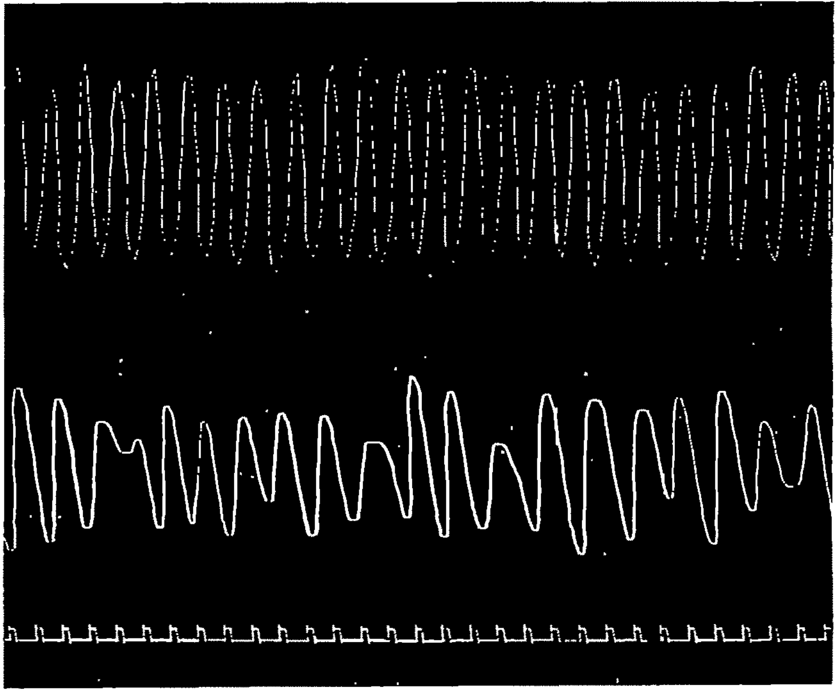

FIG. 14.—Tracings of alternating pronation and supination of the normal (above) and the ataxic arm of a patient with a right-sided lesion of the cerebellum. Time in seconds.

The range of the excursions is often irregular too; often excessive when they are not mechanically restricted as in the pronation-supination test (fig. 15), but sometimes less than normal. Failure of prompt arrest of each movement on the one hand, and its premature arrest on the other, explain these inequalities in range.

But loss of postural tone adds to the difficulties in performing alternating movements. During rapid pronation-supination of the normal forearm the upper arm remains steadily fixed in position, but the affected limb sways about passively and irregularly from the shoulder with the result that the forearm has not a stable base on which to move. This naturally increases the difficulty in moving it rapidly and accurately. Noica has also drawn attention to the important rôle played by defective fixation of the proximal segments in dysdiadochokinesis.

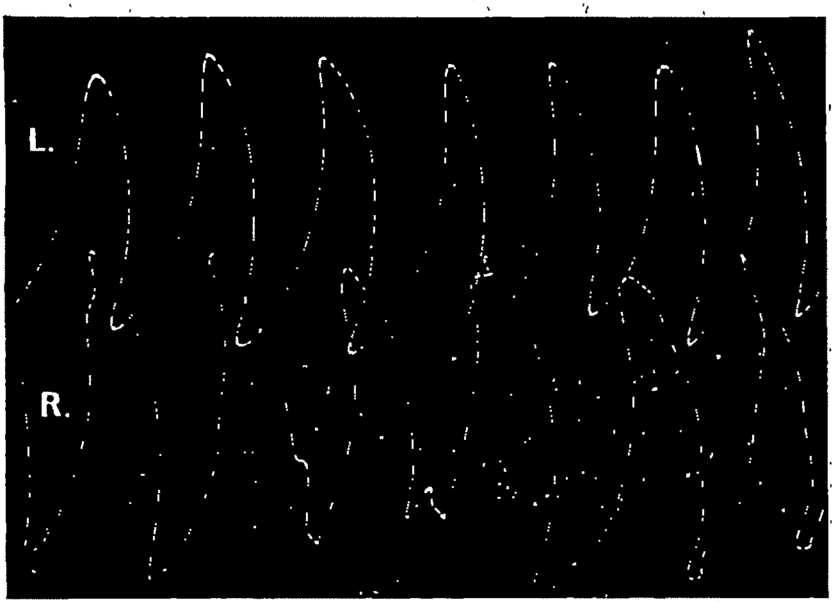

FIG. 15.—Alternating flexion and extension of the elbow of the normal (L.) and ataxic arm (R.), recorded in succession on a moving camera plate by interrupted lights attached to the index fingers. Each flash corresponds to 0·04 second.

When alternating movements are prolonged, and particularly when the patient is urged to persist in them, the excursions become laboured and forced, the limb tires rapidly and it may eventually come to a standstill as if held up (fig. 16). This is not wholly due to fatigue, for if the limb is handled all its muscles, and not only those actively concerned in the action, may be found rigidly contracted, or the original movement may be replaced or complicated by others. In the pronation-supination test the fingers and wrist may straighten and bend alternately, the forearm may flex and extend, or the arm may adduct and abduct at the shoulder more or less synchronously with the movements which are desired. Muscular contractions spread aimlessly over the limb. This seems to be a result of excess and confusion of voluntary innervation in the effort to keep up the rhythm of movement when the rate, force and range of the separate excursions and the rapid reversals of direction are not under control. The fact that diversion of attention, as by the simultaneous performance of the same or of other movements by the opposite limb, increases the irregularities indicates how dependent the rhythm of movement is on concentrated effort when cerebellar function is defective. One intelligent and observant patient remarked, "The movements of my left arm are done subconsciously, but I have to think out each movement of the right (affected) arm. I come to a dead stop in turning and have to think before I start again." It is significant that practice may improve the performance of the test.

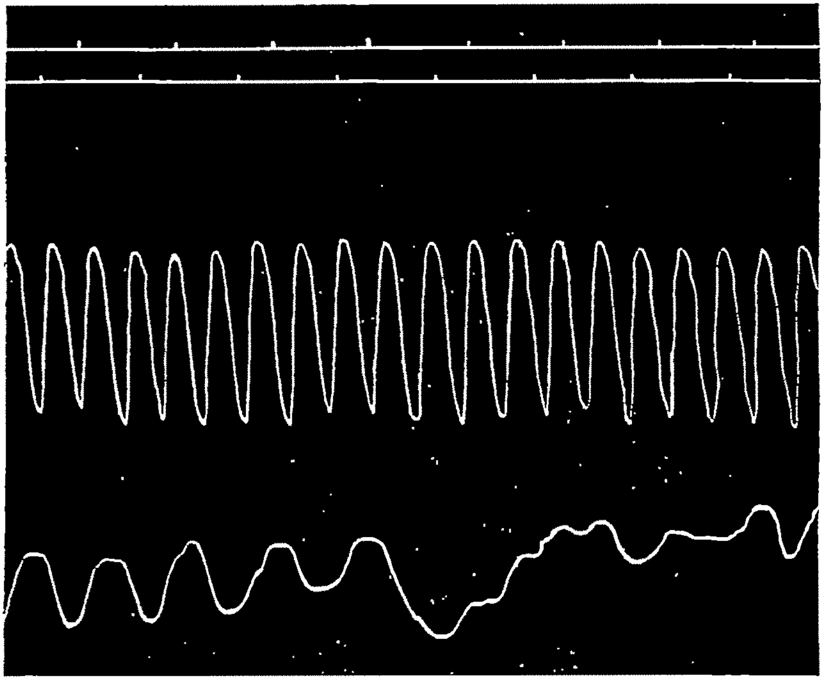

FIG. 16.—Tracings of rapid pronation-supination. The movements of the affected arm (below) were for a time regular though slower and of smaller amplitude than the normal, but grew irregular and the arm became more or less fixed in supination.

A somewhat similar difficulty in executing alternating movements results from disease of the basal ganglia. To this fact we shall recur later.

Asynergy.—The term asynergy has been used so indiscriminately in the literature on the cerebellum that it is frequently difficult to decide the exact significance given to it. To some, as Tilney and Pike, Sager and Leiri, it means merely a disturbance in the normal co-operation of agonists and antagonists; others employ it in Babinski's original sense to signify a lack of co-ordination between wider groups of muscles, including those which should fix segments of a moving limb. In the latter sense the term is unnecessary as it would include symptoms of different origins. The question whether there is a specific disturbance in the normal relations of agonists and antagonists is more important. As Walshe (1927) has pointed out this relation is at the very foundation of the simplest reflexes and it is therefore improbable that it is in any way subject to cerebellar influence. Bremer concludes that no such disturbance has been proven, and Pollock and Davis have shown that it is not affected by removal of the cerebellum in animals. In his study on action currents Altenburger also found in man no alterations in the relations of agonists and antagonists during movement. My own observations indicate that no such disturbance exists in sufficient degree to play a part in the symptomatology of "cerebellar ataxia." Absence of the steadying influence which tonic antagonists normally exert on the prime movers in deliberate and accurate movements is, however, an important element, but this is merely a result of the general hypotonicity.

I have studied the relations of such simple synergies as extension of the wrist on flexion of the fingers, but though tracings show that when the fingers suddenly close wrist extension is less regular than normal, this does not appear to be an important or specific factor of "cerebellar ataxia."

Gait.—Owing to the wide distribution of these disturbances over the musculature of the trunk and limbs the irregularities of movement are greater the more complicated the latter is, and the larger the number of muscle groups employed in it. Abnormalities of gait, for instance, are often so prominent that an apparatus for the maintenance of equilibrium, or a special co-ordinating function for locomotion, have been assumed to exist in the cerebellum, but examination shows that they are a natural consequence of the same fundamental troubles which involve the whole motor system.

Nystagmus.—Although nystagmus is not common after ablation of the cerebellum in animals, and when observed has been attributed to injury of the vestibular nuclei or of other structures in the brain-stem, there is no doubt that in man it is a common and direct result of cerebellar disease. Its essential feature is that the eyes fail to maintain postures and gradually swing towards their position of rest (slow phase), from which they are brought back by abrupt contractions of the oculogyric muscles (quick phase). This failure of posture is in every way comparable to that present in the rest of the motor system, but exceeds it in degree. The reason of this may be that the cerebellum has intimate anatomical and functional connections with the vestibular apparatus, and the latter has a dominant influence on ocular movements and postures.

Disturbances of associated and automatic movements.—A common symptom in even slight lesions of one side of the cerebellum is a failure of the ipsilateral arm to swing actively in walking synchronously with advance of the opposite leg; it hangs limply by the side or sways passively with movements of the shoulder. In progressive disease this is one of the earliest symptoms to appear, and it is usually the last to go on recovery. It cannot be readily explained by any of the primary motor disturbances with which we have already dealt, and may probably be regarded as a primary and fundamental symptom. It is also a feature of disease characterized by Parkinsonism due to destructive lesions of the corpus striatum; here it has been attributed to muscular rigidity, but as it may appear before onset of the rigidity this explanation is not adequate. The significance of such a special symptom in two conditions otherwise unlike will be discussed later.

FUNCTIONS OF THE CEREBELLUM AS REVEALED BY CLINICAL OBSERVATIONS.

From this analysis of the symptoms which result from lesions of the human cerebellum it is evident that the essential disturbances are: (1) postural hypotonia and impairment of certain reactions of the toneless muscles; (2) mild degrees of asthenia and fatigability of the muscles; (3) abnormalities in the rate, regularity and force of voluntary movements, and (4) failure of certain associated movements.

The disturbances included in each of these groups appear to be, as far as clinical examination can determine, primary or fundamental, that is not attributable to other factors. The hypotonia and defective postural adaptation are certainly elementary defects. It is possible that asthenia and fatigability are related to the hypotonic state of the muscles, but the disturbances in the rate and regularity of voluntary movement seem to be independent of it. This problem can be decided definitely only by investigation of the reactions of the hypotonic muscles by physiological methods. For the present they can be regarded as fundamental or elementary defects.

All the other symptoms included in "cerebellar ataxia," "inco-ordination" and "asynergy," are partly due to these elementary defects, in part the result of attempts of other portions of the nervous system to compensate the functions which are lost; the latter represent what Hughlings Jackson has called "forcing of other movements by overactivity of perfectly healthy nervous arrangements" (1888).

An analysis of the defect symptoms certainly affords no ground for assuming that the cerebellum contains a special centre for co-ordination, or that its function is the "co-ordination of motion" (Cobb). The inco-ordination which is undoubtedly associated with cerebellar disease is due to more elementary disorders which impair the correct and harmonious execution of movements. In Hughlings Jackson's words, "It is only by entertaining vague notions about 'a co-ordination centre' (the lineal descendant of 'faculty of co-ordination') that we can speak of a destructive lesion of the cerebellum as causing inco-ordination of locomotion" (1888).

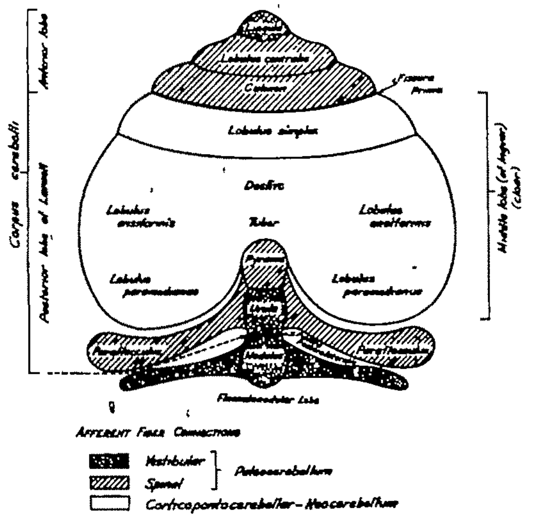

FIG. 17.—A diagram of the macaque cerebellum after Larsell (from Botterell and Fulton).

The problem then arises as to how the cerebellum normally assures postural tone, the grading and regulation of the rate and force of muscular contractions, and the execution of synkinesic automatic activities. In attempting to solve this problem it is necessary to recall its main connections with the rest of the nervous system.

Sherrington's term, "the head ganglion of the proprioceptive system," emphasizes the important influx to the cerebellum of afferent impulses which are largely concerned in posture. Through the spinocerebellar tracts and from the dorsal columns of the cord it receives messages from the deeper structures of the limbs and trunk, and from the vestibular apparatus, which plays such a large part in the postural reflexes, there is a constant stream of impressions. These spinal and vestibular impulses reach only the anterior and posterior segments of the cerebellum which represent the oldest parts of this organ (the palæocerebellum) (Larsell) (fig. 17). On the other hand by means of several paths through the correlation centres with which it is intimately connected this part of the cerebellum can send efferent impulses to the brain-stem and spinal cord.

But in man and the primates the palæocerebellum is a relatively insignificant part of the whole. The large lateral lobes and the middle portions of the vermis, which constitute the so-called neocerebellum, are newer structures with different anatomical connections and it may be assumed they have different functional relations. They have developed parallel with the growth of the fore-brain, and especially of the cerebral cortex, during that stage of evolution when the fore-limbs no longer required for stance and locomotion became available for delicate purposive movements (Brouwer and Biemond). It is from the cerebral cortex that their main afferents come by way of the cortico-pontine tracts and collaterals of the cortico-spinal bundles. Their chief efferent fibres, which arise in the neocerebellar nuclei, also pass cerebralwards through the superior peduncles and terminate mainly in the thalamus, which in its turn is intimately connected with the corpus striatum and other basal ganglia, as well as with the cortex.

It is, however, unlikely that a functional distinction comparable to this anatomical division exists between the so-called palæocerebellum and neocerebellum, and that the proprioceptive impulses from the spinal cord and vestibular apparatus, though they arrive in the former, have no influence on the latter. The uniform structure of the cerebellar cortex and the complex association fibres between different portions of it are strongly in favour of a uniformity, though not necessarily an identity, of function within it.

The neocerebellum of man, which owing to its size and position is most commonly involved by such local lesions as produce "cerebellar ataxia," has therefore predominantly cerebral relations, and it is probable that in the sense of these relations its functions must be sought (Walshe, 1927). Physiological experiments have provided evidence of this relationship; Russell and Rossi independently found that electrical stimulation of the surface of the neocerebellum alters the threshold of excitability of the motor area of the opposite cerebral cortex, and Aring and Fulton observed "dramatic accentuation" of cerebellar signs when area 6a of the opposite frontal lobe was removed from animals in which these signs had decreased some time after extirpation of one side of the cerebellum. The predominance of symptoms of cerebellar defect in voluntary movement also indicates that it influences directly cerebral mechanisms which excite and integrate such movements rather than the reflex apparatus of the brain-stem and spinal cord; the latter, when isolated from the fore-brain, are in fact unaffected by ablation of the cerebellum.

It is a striking feature of acute cerebellar injury that its symptoms gradually decrease in intensity and may in time disappear. This fact has been universally recognized and has been explained by compensation by intact parts of the cerebellum and by other parts of the nervous system. But even in the acute stages of disease the disturbances may be to some extent reduced by training and by concentrated effort; for instance, a man who is unable to pronate or supinate his forearm, or flex and extend his fingers rapidly, may learn by repeated attempts to do so, and by practice may succeed in controlling to some extent the irregular movements of his ataxic limbs. As learning is predominantly a function of the higher levels of the nervous system, the cortex, and especially those parts of it concerned in the integration of voluntary movement, probably play a large part in compensation. There is further evidence of this in the facts that cerebellar ataxia becomes greater when attention is diverted from the active limb, and that the irregularities of movement increase after the administration of alcohol and narcotic drugs which depress attention (Holmes, 1918).

Hypotonia is certainly most prominent when the lateral lobes, which have cerebral connections, are injured, in fact according to several authors (Rademaker, Bremer, Sager) in lower animals rigidity of muscles follows removal of the palæocerebellum. This suggests that the neocerebellum may influence muscular tone by its action on the fore-brain.

Tone, it is true, depends on segmental reflexes, but Sherrington has shown that it may be modified by suprasegmental centres. As Bremer has pointed out, the cerebralward transfer of phasic motion necessitates a corresponding subordination of postural tone to the activity of the cortex of the fore-brain. By virtue of the proprioceptive impulses which it receives from all peripheral structures concerned in posture and in movement the cerebellum is in a position to send to the fore-brain an integrated influx which may serve in the control and distribution of muscular tone. As I wrote in my Croonian Lecture, the cerebellum in this way "helps to maintain and regulate the distribution of postural tone, and by its influence on the fore-brain it aids in the regulation and the co-ordination of the modifications of tone in the necessary contractions and relaxations of muscles during movement" (1922).

The activities of the higher and less organized nervous centres are not dependent in the same degree as the lower on afferent impulses from any one source; when some are lost they may be replaced or compensated by impulses of other origin. This may be the explanation of the absence of obvious hypotonia in chronic and in stationary diseases of the cerebellum; its tonic functions are compensated by the activity of other centres, possibly by the cortex of the frontal lobe as Aring and Fulton have suggested.

Through the thalamus the cerebellum is also connected with the basal ganglia, including the substantia nigra, nucleus ruber and other subcortical centres, that is with those structures which belong to the so-called extra-pyramidal motor system. Though the functions of these masses of grey matter are still obscure there is general agreement that they are concerned in regulation of postural tone and in certain automatic activities and associated movements. Experimental physiology has as yet contributed little to our knowledge of the part they take in movement, but evidences of the important rôle they play in posture and in motor activity is presented from the clinical side by the disturbances of tone, irregularities of movement and spontaneous movements which characterize negative lesions of them. One of their functions seems to be to inhibit and control the tonic mechanisms of the brain-stem and spinal cord; when they are separated from the more caudal parts of the nervous system decerebrate rigidity results. The afferent impulses which regulate this activity may come from many sources, but it is probable that a cerebello-thalamic influx is one of the most important. During voluntary movement this cerebellar influx may be modified by the cerebral cortex through the cortico-pontine tracts; the size of the latter and their development parallel with the transference of volitional innervation to the cerebral cortex suggest they have an important influence in movements initiated in the cortex.

While the rigidity and exaggerated postural fixation of extrapyramidal disease can be regarded as "corresponding opposites" (Jackson) of cerebellar hypotonia, the diminution of certain automatic activities, as failure of the arms to swing in walking, the static tremor which may appear during maintenance of posture, the poverty of automatic movements, the slowness of motion and the difficulty in performing alternate movements, are symptoms common to disease of both the extra-pyramidal system and the cerebellum, and indicate a functional relationship between these two organs.

On this hypothesis there is superimposed on the postural and reflex mechanisms of the brain-stem a cerebello-striato-cortical apparatus concerned in the regulation of posture and of tone during voluntary movement. By virtue of the integration of the wealth of afferents it receives from all parts of the body and from the cerbral cortex the cerebellum is a controlling part of this mechanism.

Although Sherrington has shown that postural tone may fuse with and reinforce muscular contractions otherwise excited, clinical observations suggest that the *asthenia* of volitional movement in cerebellar disease is not due to lack of this tonic support. Rossi's discovery that stimulation of the surface of the cerebellum increases the excitability of the contralateral motor cortex is in favour of the view that the cerebellum exerts a reinforcing action directly on the cerebral centres through which voluntary motion is excited. Loss of postural tone supporting voluntary contractions may, however, contribute to the tendency to tire, but Bremer's view that *fatigability* as well as feebleness of movement is a fundamental symptom and due to an asthenia of the cortico-spinal motor apparatus deprived of cerebellar reinforcement, seems more probable.

The *abnormalities in the rate and regularity of voluntary movement* cannot be explained by disturbances of the executive motor mechanisms of the brain-stem and spinal cord as when these are isolated from the forebrain removal of the cerebellum does not affect their activities. Nor can they be attributed to the toneless state of the antagonists as they appear in movements against resistance in which the opposing muscles are not actively concerned. We must therefore conclude that they are due to disorder in the cerebral mechanisms of voluntary movement, as a result of which there is a delay in initiating cortico-spinal innervation, a lack of uniformity in the intensity of corticofugal discharges and a failure to arrest or inhibit these discharges with normal promptitude.

The conclusions can be drawn that, in addition to regulating postural tone, the cerebellum reinforces or tunes up the cerebral motor apparatus, including subcortical structures with motor functions, so that they respond promptly to volitional stimuli and the impulses from them which excite muscular contractions are properly graded.

In his classical contributions to the physiology of the cerebellum Luciani described as the three symptoms of cerebellar defect: atonia, astasia and asthenia. These three symptoms occur in man as a result of acute cerebellar lesions and by them the irregularities of movement which constitute cerebellar ataxia can be fully explained.

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SOME OBSERVATIONS ON THE NATURE OF VIBRATORY SENSIBILITY.[1]

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THE nature of vibratory sensibility has long been a matter of conjecture and controversy, as revealed by the voluminous literature concerning it. The question as to whether or not it constitutes a distinct modality of sensation cannot be said to be definitely settled, it being variously stated that it is an integral part of touch, of pressure, or an entity in itself.

The central representation of vibratory sensibility seems more definitely established and must certainly be localized in the sensory cortex. It has also been shown that the pathway traverses the thalamus, while in the spinal cord it is generally conceded (Gordon, 1936) to be in the homolateral posterior columns, as shown by the loss of vibratory acuity on the homolateral side after hemisection of the cord. However, the peripheral distribution, and the type and location of the end-organs involved are far from clear, and it is with these questions that this paper concerns itself.

METHOD.

Because of the greater ease of control and measurement of the vibratory stimulus with an electromagnetic vibrator than with a tuning fork, no matter how ingeniously contrived, the former type of instrument was chosen for this work. The actual instrument used presented no departures in principle from those devised by other workers (v. Bogh (1935), Sitzepfand (1935) and Hugony (1935)). It consisted of an electro-magnet, the pole-piece of which is caused to vibrate by the passage of alternating current through the coil. This is derived from a beat-frequency oscillator capable of generating current at frequencies from 30 to 15,000 cycles per second, of essentially sine-wave form. The voltage across the coil of the electromagnet and the current through it are controlled by means of a potentio-

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[1] Work done while Dr. Newman held a Rockefeller Fellowship, Dr. Doupe a Halley-Stewart Research Fellowship, and Dr. Wilkins a Fellowship of the American College of Physicians.

meter, and measured by suitable meters. Thus both the frequency and amplitude of the stimulus are variable at will, and accurately mensurable. Since it has been shown that for a given frequency the amplitude of vibration is fairly closely proportional to the current passing through the coil, this figure in milliamperes has been used to designate the intensity of the stimulus. The pole-piece, which actually delivers the stimulus, is a square piece of metal measuring 9 by 9 mm., and is ordinarily applied to the area to be tested by holding the handle of the instrument, about 17 cm. long, at the end and allowing it to press on the skin by its own weight, thus maintaining a fairly constant pressure of about 450 grams per square centimetre. At other times, the pole-piece is just maintained in contact with the skin, without perceptibly deforming it. The first type of contact will be termed heavy, the second light. In all cases the vibratory movement is roughly perpendicular to the skin surface.

It was found by this technique that the threshold for vibratory sensibility, as measured by the intensity of stimulation at which the subject first became aware of vibration of the instrument when the current was gradually increased, remained quite constant for the same locality in the same individual from time to time, especially with heavy pressure. With light pressure the results were less constant, owing to difficulty in maintaining a constant pressure of contact. Such was the constancy of thresholds obtained, however, that there could be little doubt of changes which appeared after any experimental intervention being connected with that procedure, and not being due to chance fluctuations.

All the experiments were carried out with a frequency of 200 cycles per second as the standard stimulus. This was found to be the optimal frequency, as has been noted by other observers (v. Bogh (1935) and Sitzepfand (1935)). Both lower and higher frequencies gave higher thresholds, and with the intensities at our disposal 500 to 600 cycles was the highest that could be perceived except in the hands, and particularly in the fingers, where up to about 1,000 cycles could be discerned. In all cases where there was a change in threshold brought about by anæsthesia, all frequencies seemed to be affected to about the same degree, with no tendency for either the higher or the lower to drop out first.

PROCEDURES AND RESULTS.

For the evaluation of the results to be reported it was necessary to know the comparative thresholds for light and heavy contact in the regions used in these experiments. Table I, which gives the averages of several experiments in normal young adults, shows that for heavy contact the finger-tip was the most sensitive, then the forearm and calf, and lastly the forehead. The threshold for light contact varied in the same way, and was close to that for heavy contact in the case of the finger and forehead, but above it in the case of the forearm and calf. Little difference was found whether the contact overlay bone or muscle.

TABLE I.—AVERAGE THRESHOLD AT DIFFERENT SITES.

		Heavy contact	Light contact
Finger tip	...	0·07 milliamp.	0·10 milliamp.
Forearm	...	0·4 „	3·0 „
Calf ...	...	1·0 „	5·0 „
Forehead	...	3·5 „	5·0 „

It was also necessary to know to what degree the tissues could conduct vibrations from an insensitive to a sensitive area. To determine this, a sphygmomanometer cuff was placed around the forearm and inflated to a pressure of 200 mm. Hg for fifty minutes, which caused complete anæsthesia below the cuff. The threshold for heavy contact on the radial styloid process rose from 0·06 to 0·4, while for light contact it rose from 0·3 to 5 5, and the sensation was now referred to the region of the elbow. The capacity of the bones to act as vibrators was further shown in two cases with section of the left second, third, fourth and fifth thoracic posterior roots. In the denervated area the threshold for heavy contact was only slightly raised, and was not affected over the denervated half of the sternum.

DEEP STRUCTURES.

That vibration sense may be mediated by sensory endings in deep structures was shown in the following way. In three individuals on thirteen occasions the threshold for heavy contact was determined several times on four spots on the forearm or calf. Into one spot 3 c.c. of 2 per cent. novocain with adrenalin were injected subcutaneously so that an area of skin 3 cm. in diameter was rendered anæsthetic. The vibratory threshold was then measured repeatedly on all the spots and no rise in threshold was found on the anæsthetic one. In a few instances the threshold was lowered locally by the novocain. In five further experiments a cutaneous nerve in the forearm, calf, or thigh was anæsthetized with novocain. This did not cause any change in threshold with heavy contact in the distribution of the nerve anæsthetized, although there was complete anæsthesia of the skin.

Seven experiments were then done in an endeavour to modify the appreciation of vibration by anæsthetizing deep structures while leaving superficial sensation intact. This was done by the use of localized pressure applied by means of a clamp with one bearing surface large and the other small—the latter being placed over the nerve—or by the injection of 2 per cent. novocain and 1:60,000 adrenalin into the trunks of the ulnar and median nerves at the elbow, and the superficial peroneal nerve at the neck of the fibula. Block of the ulnar nerve at the elbow caused, among other things, paralysis of the flexor carpi ulnaris and of the medial half of the flexor profundus digitorum, and anæsthesia to all forms of sensation in the little finger. Block of the radial nerve on the anterior surface of the lateral condyle of the humerus produced paralysis of the extensor muscles of the wrist which lie on the posterior aspect of the forearm. Block of the superficial peroneal nerve caused paralysis of the peroneal group of muscles. Cutaneous sensation over these groups of paralysed muscles, however, remained intact. In these experiments two or three points over the paralysed muscles were selected, with a similar number of points over adjoining muscles to serve as controls. In the case of the ulnar nerve experiments the 2nd, 4th and 5th digits were examined. After two or three readings at each site had been taken and a reasonably steady base-line established, the blocking procedure was begun. Thereafter readings were taken at each site every ten minutes for forty to fifty minutes, at which time a maximal effect seemed to have been produced. The last two readings were then compared with the findings before the induction of the block, and the percentage rise in threshold calculated. The average rise at the sites over the paralysed muscles was 70 per cent., while the average rise at the control sites was 10 per cent. Table II sets forth the results of each experiment.

To control the possibility that the flaccidity of the paralysed muscles might have been responsible for the rise in vibratory threshold another experiment was done. Observations were made on the posterior aspect of the forearm with the underlying muscles voluntarily contracted and relaxed. No significant difference in threshold was found with the muscle in these two states.

In order to determine whether direct stimulation of the periosteum is responsible for the sensation of vibration, a large area on the anterior surface of the tibia was infiltrated with 2 per cent. novocain and adrenalin. This procedure abolished all superficial and deep sensibility in the area injected. No rise in vibratory threshold to heavy contact was found when compared with the pre-injection acuity, and to control readings on the other leg. Thus it was evident that direct stimulation of the periosteum by the stimulating instrument was not an important factor in the appreciation of vibration.

In the experiments in which the ulnar nerve was blocked, it was found that vibration sense was completely abolished in the 5th digit. This was particularly true if slight traction were exerted on the distal phalanx to prevent the conduction of vibration from bone to bone. In the 2nd and 4th digits the threshold for heavy contact was unaffected. However, on the medial side of the 4th digit, where there was loss of light touch, the threshold for light contact was raised. It was apparent from this that the preservation of the acuity of perception of vibration with heavy contact in the 2nd and 4th digits was not due to receptors lying in the skin. It was also observed that the rise in vibratory threshold in the 5th digit was, along with a diminution in postural sense, the first demonstrable effect of pressure on the ulnar nerve, and the threshold of vibratory sense had greatly risen before any paresis of the muscles was evident. The intact threshold to heavy contact on the medial side of the 4th digit and the results of a further experiment reported below showed that this loss in vibratory sense to heavy contact was not due to interference with cutaneous sensibility. The facts that the threshold had risen before any muscular weakness was evident, that vibration sense was completely abolished while many of the muscles supplying long tendons to a 5th digit had an intact innervation.

TABLE II.—VIBRATORY THRESHOLD.

Exp. No.	Procedure	Over paralysed muscle			Control		
		Average before *	Average after*	% change	Average before *	Average after *	% change
321	Novocain anæsth. ulnar N.	0·6	1·2	+100	1·0	1·4	+40
		0·5	0·7	+ 40	0·5	0·6	+20
322	Novocain anæsth. ulnar N.	1·6	2·4	+ 50	3·9	3·5	−10
					4·0	2·4	−40
					1·9	2·5	+30
					1·2	1·9	+58
324	Pressure anæsth. ulnar N.	2·0	2·1	+ 5	3·1	4·0	+29
		2·4	2·0	− 16	3·1	2·7	−13
		2·6	6·0	+130			
327	Pressure anæsth. ulnar N.	0·7	2·2	+214	1·0	1·1	+10
		0·8	1·5	+ 88	0·67	0·72	+ 7
328	Pressure anæsth. radial N.	0·15	0·32	+133	0·19	0·17	−10
		0·23	0·25	+ 8			
		0·14	0·33	+136			
326	Pressure anæsth. sup. peroneal N.	0·7	0·8	+ 14	2·0	0·75	−65
		2·8	4·6	+ 64	2·9	2·8	− 3
	on release	0·8	0·8	0			
325	Pressure anæsth, sup. peroneal N.	3·0	5·2	+ 73	4·2	5·1	+21

* Figures express in milliamps the intensity of the vibratory sensibility.

and that no rise in threshold occurred in the 2nd and 4th digits whose small muscles were also paralysed, indicated that the sensation of vibration was partly mediated in the finger by structures lying deeply within the finger itself and unassociated with muscles and tendons.

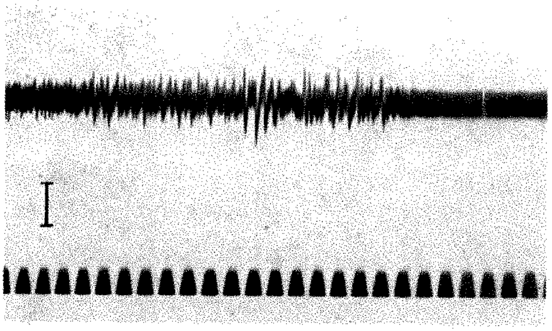
SUPERFICIAL STRUCTURES.

When the vibrating surface was applied so that it was just in contact with the skin the threshold was as a rule much higher than that with heavy contact. This was particularly true in the limbs at those sites where there was much subcutaneous tissue. It has already been stated that on the finger-tips and forehead there was little difference in threshold between the two types of contact. The question therefore arose as to whether the sensation of vibration could be mediated by way of receptors in the skin, or depended entirely on the transmission of the vibrations to deeper structures. The following observations bear on this question.

To determine if receptors were located in the skin which could respond at frequencies usually employed in testing vibration sense, Dr. G. L. Brown kindly performed the following experiment. A purely cutaneous branch of the saphenous nerve of a cat was dissected out, and placed across two electrodes. Action potentials from this nerve were suitably amplified and recorded on moving bromide paper, a Matthews oscillograph being used. Light stroking of the area of skin innervated by this nerve produced discharges as shown in fig. 1. The insulated base of a tuning fork with a frequency of 64 cycles per second was then lightly applied to the area, with production of large action potentials at the same frequency as the vibrations of the fork, as seen in fig. 2. Even larger potentials were produced when an arm rather than the base of the fork was used to stimulate the skin (fig. 3). Similar potentials at the same frequency as the vibrations of a fork of 450 cycles were also obtained. The same potentials were obtained when the bit of skin was dissected free from the leg (fig. 4). Crushing the nerve abolished the potentials; furthermore, they did not appear when a piece of moist thread was substituted for the nerve. It seemed probable, therefore, that the quality of vibration might be recognized by receptors lying in the skin, which initiate rhythmical action potentials when subjected to the stimulus of the tuning fork.

In one subject the 3rd digit was rendered anæsthetic by iontophoresis with 2 per cent. cocaine, causing a sensory loss to pin-prick and light touch, without disturbance of proprioceptive acuity. The threshold to vibration with heavy contact remained unchanged, and similar to that in the second

PLATE I.



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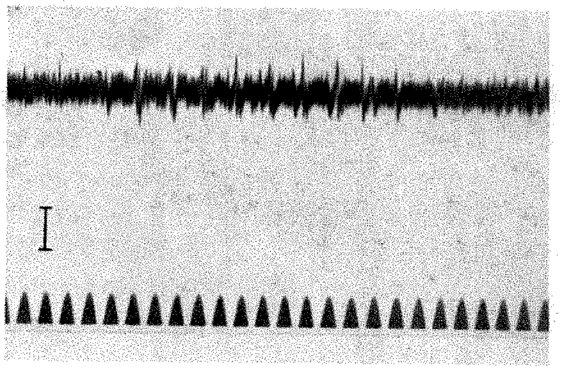

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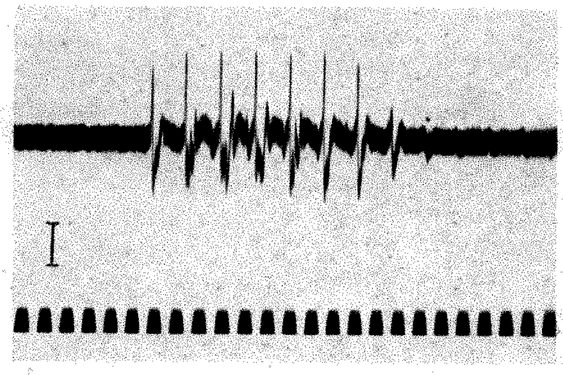

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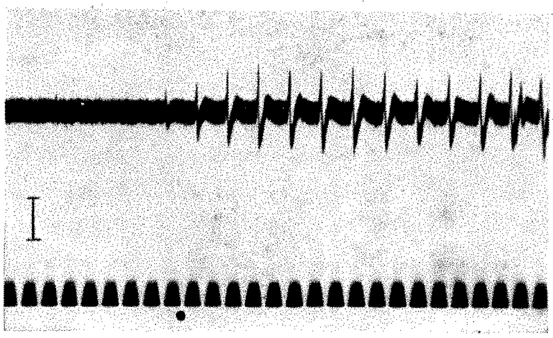

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Action potentials from a cutaneous nerve of the cat. Calibration shows deflection caused by 20 microvolts. Direction of negative deflection is upwards. Time in 1/100 seconds.

Fig. 1.—Response to stroking skin.
Fig. 2.—Response to stimulation by base of 64 cycle tuning fork.
Fig. 3.—Response to stimulation by arm of 64 cycle tuning fork.
Fig. 4.—Response to stimulation of isolated skin by arm of 64 cycle tuning fork.

To illustrate article by H. W. Newman, J. Doupe and R. W. Wilkins.

finger. The threshold for light contact was raised, but progressively returned to the original level as cutaneous sensation returned. However, anæsthetization of the skin of the forearm by the local injection of 2 per cent. novocain and adrenalin was found to cause only irregularly a rise in threshold to light contact. That this might be attributed to the great sensitivity of the deep receptors in this region was shown by an experiment in which the ulnar nerve was anæsthetized by pressure at the elbow. On sites overlying the paralysed muscles in the forearm, but on unaffected skin, the threshold to both heavy and light contact rose slightly, presumably due to anæsthesia of the deep receptors. Then, during the period of the pressure block, 2 per cent. novocain was injected subcutaneously into one of the sites over a paralysed muscle. This resulted in a further marked rise in the threshold to light contact. It was thus seen that only when the deep receptors, with their great sensitivity, are anæsthetized does the cutaneous appreciation of vibration become evident.

In the upper arm a slightly different relationship between the sensitivity of the deep and superficial receptors seems to exist. Thus in a subject who had had a section of the left 5th cervical dorsal root there was a very marked rise in the threshold to light contact over an oval area 10 by 5 cm. on the lateral aspect of the upper arm co-extensive with the area for diminished touch. However, no rise in threshold for heavy pressure was demonstrable, even over the partially paralysed and wasted deltoid.

On the forehead and tongue results differing from those on the forearm were obtained. In these situations the threshold for light and heavy contact was about equal, and was similar to that for light contact on the forearm. Anæsthetization of the skin of the forehead by the injection of novocain, or of the mucous membrane of the tongue by the topical application of cocaine, raised the threshold to both types of stimulation. In these regions, therefore, the deep receptors, if they be present, have a comparatively high threshold. Observations on a subject who had had a section of the sensory root of the left 5th cranial nerve confirmed this deduction. It was found that an exceedingly high threshold to both light and heavy contact existed on the left side of the head and tongue. This high threshold persisted unchanged to within 3 mm. of the midline, despite the fact that vibration was mechanically transmitted and could easily be detected by the observer at points all over the skull. Thus in this situation mechanical transmission by bone seems not to be a factor. This is in contrast to the experiment reported on the forearm, where stimulation at the anæsthetized wrist could be felt at the elbow.

AFFERENT PATHWAYS.

The peripheral fibres conducting the sensation of vibration from light and heavy contact appeared to be of the same size, and similar to those mediating touch and passive movement. This was shown by the observation that the sensitivity to vibration, touch, and passive movement was very easily affected by pressure on the nerve, but disappeared comparatively late when novocain was the anæsthetizing agent. However, an essential difference between the appreciation of vibration according to whether light or heavy contact were employed was demonstrated in subjects with lesions of the spinal cord. In two cases of unilateral section of the spino-thalamic tract no difference in threshold to either type of stimulus between the normal and anæsthetic sides was evident. However, the sensation produced by light contact was subjectively different, being less "sharp" on the analgesic side, and corresponded to the change in appreciation of light touch. The sensation with heavy contact was not altered. In a subject with disseminated sclerosis who had a typical Brown-Séquard syndrome, vibration sense to heavy contact was lost in the lower limb where appreciation of passive movement was defective. However, at both great toes vibration sense to light contact was normal, as was the appreciation of light touch.

DISCUSSION.

In presenting the above results several deductions have already been made. It has been pointed out that the sensation of vibration can be mediated by receptors lying both in the skin and in the deeper tissues. The relative acuity of these two sets of receptors has been found to vary in different parts of the body.

A consistent rise in threshold to vibratory stimulation over muscles, the nerve supply of which had been functionally interrupted, indicates that there are receptors for this sensation in muscle itself. Periosteum is probably not an important factor, as shown by the experiment in which it was anæsthetized over the tibia without any loss of vibratory acuity. The importance of bones in mechanically transmitting the vibrations to the sensitive structures has been demonstrated in the experiment where the wrist was rendered anæsthetic. The experiment with ulnar nerve block indicates that tendons are probably not an important factor, for the tendon innervation to the little finger was largely intact, yet vibration was not perceived when mechanical transmission by the bones was interrupted. It has also been shown that some of the deep receptors are not associated with muscles.

The vibratory sensation from the deep receptors in the 5th digit has been shown to be affected similarly as the sensation of passive movement when the ulnar nerve was anæsthetized. Stopford (1930) has shown, and we have confirmed his observations, that passive movements are recognized at the joints of a digit the muscles and tendons to which have been deprived of their nervous connections. The recognition of vibration in such digits was similarly unaffected. Ecklin and Fessard (1937) have recorded from nerves to muscles, in the cat, action potentials of a frequency synchronous with the vibrations of a tuning fork applied to the muscles or their tendons. It was their opinion that stretch receptors, which are proprioceptive in nature and at least partially responsible for the perception of passive movement, were the source of the electrical activity demonstrated. The present results also indicate that the sensation of vibration is in part dependent on receptors in muscle. The peripheral nerve fibres conveying the sensations of vibration and passive movement are similarly susceptible to compression and novocain. Lesions of the posterior columns abolish the perception of both passive movement and vibration from deep structures, while lesions of the spinothalamic tract do not affect it.

Thus all the evidence seems to indicate that there is a very close relationship between the senses of vibration and of passive movement. So similar, indeed, are the sites of their peripheral receptors, the characteristics of the nerve fibres, and the central pathways, that it seems probable that they are mere variants of a single mode of sensibility. However, it must be remembered that purely cutaneous stimulation has also been shown to be appreciated as vibration. The experiments carried out by Brown and recorded above show that certain potentials of a similar character to those produced by Ecklin and Fessard could be obtained from a nerve to an isolated piece of skin. It is probable that this cutaneous appreciation of vibration bears the same relationship to touch as the appreciation by the deeper tissues does to passive movement. Vibration cannot, therefore, be said to be a specific modality. The sensation is the result of rapid repetitive stimulation of touch or proprioceptive endings.

CONCLUSION.

It has been shown that the sensation of vibration may proceed from stimulation of receptors in the skin and in the deeper structures. It is probable that the receptors in the skin are the same as those concerned with the sensation of touch, while those in the deeper tissues are closely related to, if not identical with, the receptors mediating the sense of passive movement.

THE SYSTEMIZATION AND CENTRAL CONNECTIONS OF THE SPINAL TRACT AND NUCLEUS OF THE TRIGEMINAL NERVE.

A CLINICAL AND PATHOLOGICAL STUDY

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INTRODUCTION.

The nuclei of the trigeminal nerve extend from the most cephalad level of the midbrain to the second cervical segment of the spinal cord and are at every level linked to secondary afferent and efferent neurones. It is therefore apparent how greatly they are exposed to morbid processes and how diverse are the symptoms that may result.

Despite the thoroughness with which the anatomy of the principal fibre tracts was worked out during the closing years of the last century certain obscurities still remain, particularly in regard to the extent and quality of the representation within the spinal tract and its nucleus and to the exact position of the central trigeminal pathway. With certain exceptions presently to be specified these problems have not evoked much inquiry of recent years, and the time seems opportune for their re-examination. Before proceeding to an analysis of the clinical and pathological material which forms the basis of these investigations it will be advisable to give a review of past and current opinions and to attempt a critical assessment of the clinical, pathological and experimental evidence on which they were founded.

Historical Review.

The probable segmental representation of the spinal tract and nucleus of the trigeminal nerve.—Bregmann (1892) carried out differential section of the sensory root in rabbits and studied the resulting degeneration by the Marchi technique, and arrived at the following conclusions:—

Within the spinal tract the fibres from the mandibular nerve occupy the most dorsal and those from the ophthalmic nerve the most ventral part of the tract. The fibres from the maxillary nerve lie in an intermediate position. Further, the sets of fibres from the three divisions end at separate levels. The fibres from the ophthalmic nerve end at about the second cervical segment in the most caudal part of the spinal tract. The fibres from the maxillary nerve terminate rather more cephalad but a few descend as low as the first cervical segment. The fibres from the mandibular nerve end in the upper part of the medulla oblongata. From this summary it will be seen that the three divisions of the trigeminal nerve end at levels which are in the inverse order to the peripheral distribution. Wallenberg (1896), in an experimental study on the position of the central trigeminal tracts, produced lesions at various levels of the spinal tract in rabbits and his conclusions were in agreement with those of Bregmann.

Bochenek (1901) avulsed the peripheral divisions of the trigeminal nerve in two rabbits and, at the end of sixty days, examined the brain stem by the Marchi technique. He confirmed Bregmann's findings in regard to the relative position taken up by the three divisions within the spinal tract, but he found no evidence that the fibres from the three divisions ended at distinct levels and, after avulsion of the mandibular nerve, he traced degenerated fibres to the level of the first cervical segment. His results cannot escape criticism. In the first place it is unwarranted to assume that avulsion of one peripheral division will lead to no more than selective injury to the ganglion cells of that division, it may possibly have led to more widespread damage within the trigeminal ganglion and there is no evidence that Bochenek examined this. In the second place Bochenek did not examine the brain stems serially and he made no examination of the second cervical segment of the spinal cord.

Spiller and Frazier (1901) carried out experiments bearing on this problem in order to show that the operation of sensory root section was more satisfactory than excision of the trigeminal ganglion for the cure of trigeminal neuralgia, and to this end it was necessary to show that regeneration did not occur after division of the sensory root. They divided the sensory root in dogs, and Spiller traced the resulting degeneration in the spinal tract. In some of the dogs Frazier had been able to spare the ophthalmic fibres and, on the basis of the resulting partial degeneration in the spinal tract, Spiller affirmed that the fibres from the three divisions occupied definite areas in the spinal tract, exactly as Bregmann and Bochenek had shown in the rabbit. Their results threw no light on the problem of the levels at which the fibres from the three divisions terminate.

Van Valkenburg (1911) found that in all types of vertebrate the ventrally placed fibres in the spinal tract mediated impulses from the integument of the anterior end of the head and that this ventral contingent of fibres extended furthest caudalward. The dorsally placed fibres were related to the mandibular region. They terminated cephalad of the ventral fibres and their point of termination was, to a great extent, determined by the terminal regions of viscerosensory and visceromotor nerves. Van Valkenburg's views were later supported by Frazier (1929), who stressed the essential independence of the ophthalmic nerve despite its fusion with the other peripheral divisions in the trigeminal ganglion. Further support was given by Kappers (1936) who stated that in most vertebrates the fibres from the ophthalmic nerve lie most ventral in the spinal tract and extend furthest in a caudal direction, even reaching the spinal cord. The maxillo-mandibular fibres, on the other hand, terminate in the medulla oblongata. Thus, he stated, stimulation on the top of the head leads to motor responses from the trunk and limbs while stimuli from the mouth region find expression in movements of the face and jaws through the innervation of cranial nerves.

The clinical approach to the problem began with the publication by Wallenberg (1895) of a case of occlusion of the posterior inferior cerebellar artery. The sensory loss in the trigeminal area in this case led him to adopt the view that in man the representation of the peripheral divisions within the spinal tract was similar to that described by Bregmann in the rabbit.

A different view of the segmental representation within the spinal tract was put forward by von Sölder (1899) and Schlesinger (1899, 1902) from a consideration of the distribution of sensory loss in syringobulbia. Schlesinger's views were founded on an examination of fifty-six cases of which eighteen came to post-mortem examination. In a purely clinical study von Sölder had stated that extension of the syringomyelic process from the second cervical segment to the spinal tract and nucleus of the trigeminal nerve caused sensory loss to appear first on the scalp. As the lesion extended cephalad the anterior border of the area of sensory loss advanced towards the nose and mouth. Schlesinger confirmed this observation. He postulated that the fibres from the fronto-cranial territory of the ophthalmic nerve terminated in the most caudal part of the spinal tract. The fibres of the mandibular nerve terminated at a slightly higher level and those from the maxillary nerve higher still. Finally the fibres from the nasal portion of the ophthalmic nerve terminated highest of all. From the clinical findings in syringobulbia and vascular lesions of the brain stem Kutner and Kramer (1907) arrived at similar conclusions. It is worthy of note that in those cases in which the lesion was vascular in origin the distribution of the sensory loss did not conform to von Sölder's and Schlesinger's hypothesis.

Spiller (1908) reported two cases of occlusion of the posterior inferior cerebellar artery in one of which post-mortem examination was obtained. He considered that the representation within the spinal tract was in terms of the peripheral divisions and that a lesion of the lowest part of the spinal tract and nucleus would lead to analgesia in the territory of the ophthalmic nerve. If the lesion involved the lower two-thirds of the spinal tract and nucleus then analgesia in the territory of the maxillary nerve would be superadded.

Dejerine (1914) stated that the representation in the spinal tract from below upwards was in terms of concentric zones which converged on the bucconasal orifices. It will be seen, however, that this is merely a slight variation of von Sölder's and Schlesinger's views and the diagram which he gave in illustration is identical with that figured in Schlesinger's monograph. It is quite clear (and Dejerine fully admitted it) that this hypothesis of concentric zones was based exclusively on the findings in syringobulbia. This same hypothesis was put forward by Woods (1913) in explanation of the distribution of the sensory loss which he had encountered in two cases of syringobulbia. Autopsy was obtained in only one of these and there were bilateral cavities in the medulla oblongata in the usual situation (in the formatio reticularis and in the plane of the intramedullary fibres of the glossopharyngeal and vagal nerves and extending cephalad almost to the pons). The spinal tracts and nuclei were stated to have been unaffected either by cavitation or gliosis. The analgesia on the face, which spared the upper lip and perinasal region, was attributed to an interruption of the secondary sensory neurone. The brain stem was not examined in serial section apparently but neither cavity was continuous in its vertical extent, and bridges of normal tissue intervened at several places. Stopford (1924), from the study of the blood supply of the pons and medulla oblongata and of cases of occlusion of the posterior inferior cerebellar artery, stated that " there is strong anatomical and clinical evidence in support of the view that the most cephalic part of the spinal nucleus of the trigeminal receives fibres from the anterior maxillary division and it appears highly probable that the intermediate part is connected with the superior maxillary division; whilst the ophthalmic division terminates in the caudal part." The two anatomically verified cases of syringobulbia reported by Taylor, Greenfield and Martin (1922) may be cited as evidence that the sensory loss in this disease by no means always invades the face in the manner regarded as typical by Schlesinger and Dejerine. In both these cases the analgesia and thermanæsthesia invaded the trigeminal area from above downwards and, from the beginning, the area of sensory loss extended to the midline of the face. Jonesco-Sisesti (1932), basing his conclusions on eleven cases of syringobulbia with four post-mortem examinations, stated that the territory of the ophthalmic nerve is the most frequently and earliest affected. Next in order of frequency the maxillary and mandibular nerves become affected. He attributed the early appearance of sensory loss in the territory of the ophthalmic nerve to the destruction by cavitation of the most ventral fibres of the spinal tract. A critical examination shows that this is not a satisfactory explanation of the type of sensory loss present in his cases. While in many instances the most ventral fibres in the spinal tract were most severely affected, in an equal number of cases the lateral extremity of the cavity fell short of the periphery and in such instances the most ventrally placed fibres actually appeared least affected. Furthermore this hypothesis takes no account of the possible effect of the cavity on the second sensory neurone although the characteristic dorsally placed cavity, lying obliquely between the 4th ventricle and the point of emergence of the glossopharyngeal and vagal nerves, must bar the passage of the second sensory neurone. Finally this hypothesis fails to take into account the possible effects of the gliosis which always surrounds the actual cavity.

Recently Sjöqvist (1937) has made clinical observations following section of the spinal tract in man. In four patients suffering from trigeminal neuralgia he made a horizontal incision into the spinal tract in a plane situated midway between the calamus and the junction of the medulla oblongata with the pons. The incision was placed just caudal to the most caudal rootlet of the vagus and extended into the medulla oblongata to a depth of 3·5 mm. Subsequently the patients showed analgesia and thermanæsthesia accurately limited to the territories of the ophthalmic and maxillary nerves. In some there was a light hypoalgesia in the territory of the mandibular nerve. These results do not give absolute proof that that part of the spinal nucleus related to the mandibular nerve lies at or just cephalad to the plane of the section, for it is possible that the most dorsal fibres in the spinal tract were preserved. Only a dorsal prolongation of the section, to include a part at least of the inferior cerebellar peduncle, would ensure that the whole of the spinal tract was cut. Nevertheless Sjöqvist's observations afford the strongest possible evidence in favour of the view that the segmental representation in the spinal tract is in terms of the peripheral divisions and that the order is inverted. They are incompatible with the view that the representation is in terms of concentric zones or circles which converge on the nose and mouth. The problem concerning the level at which the mandibular fibres terminate now seems to have been decided, for, in a more recent investigation, Sjöqvist (1938) has succeeded in obtaining analgesia of the whole trigeminal area by means of an incision into the spinal tract at the mid-olivary level.

An examination of general neuroanatomical and neurological writings discloses, as might be expected, a striking lack of uniformity in regard to the account of the probable segmental representation in the spinal tract. Winkler (1921), in an account of the structure of the spinal tract and nucleus, agreed with Bregmann's conclusions and considered that they applied in man. He maintains that the substantia gelatinosa proper does not extend higher than the most cephalad rootlets of the glossopharyngeus. Between this plane and the main sensory nucleus he recognizes a distinct nuclear mass ("nucleus b") morphologically identical with a part of the main sensory nucleus. This differentiation of the spinal nucleus adds to the complexities of the problems which the spinal tract and nucleus present. As yet there does not appear to have been any attempt to correlate this anatomical differentiation with normal and pathological function.

It is interesting to observe that those authors who have approached the problems of the spinal tract from the clinical standpoint accept the view first advanced by von Sölder and Schlesinger, and have based their views on the segmental representation in the spinal tract on the findings in syringobulbia, but no case of syringobulbia without complete histological examination should be admitted as positive evidence in favour of either hypothesis.

Those anatomists who have studied vascular lesions of the brain stem have never subscribed to the hypothesis of representation in terms of concentric zones and a search of the literature has failed to disclose any instance of vascular disease in which the sensory loss on the face lent support to this hypothesis.

The qualities of sensation mediated by the spinal tract of the trigeminal *nerve.*—Hun (1897) reported a typical example of occlusion of the posterior inferior cerebellar artery. There was analgesia and thermanæsthesia on the left side of the face with a crossed analgesia and thermanæsthesia on the trunk and limbs. Tactile sensibility was everywhere normal. The patient survived for three years and during this time the sensory disturbances on the face remained unaltered. Post-mortem examination showed the characteristic softening in the retro-olivary region. From these observations Hun postulated that the fibres of the sensory root of the trigeminal nerve on entering the pons are grouped in functional divisions and that impulses underlying pain and temperature pass in the spinal tract whilst touch is mediated by fibres passing to the main sensory nucleus. Subsequent reports of examples of occlusion of the posterior inferior cerebellar artery have almost always supported this view. Spiller (1915), in a presumed case of disseminated sclerosis, found gross tactile anæsthesia over the entire left side of the face with analgesia and thermanæsthesia on the entire right half of the body. He localized the lesion in the left main sensory trigeminal nucleus and with sparing of the left spinal tract (there was a very light thermanæsthesia over the territory of the left ophthalmic nerve). The interest in this case lies in the fact that pain and thermal sensibility were preserved together with complete tactile anæsthesia, thus providing strong evidence that the main sensory nucleus is the sole synaptic junction for tactile impulses. On the other hand anatomical studies have given presumptive evidence that touch is mediated by both the main sensory and spinal nuclei. Cajal (1909), Gerard (1923) and Windle (1926) have shown that, in the fœtal mouse and pig, the majority of the fibres of the trigeminal nerve on entering the pons divide into ascending and descending branches. The ascending branches end almost at once in the main sensory nucleus and the descending branches pass downwards to constitute the spinal tract. It is plain that a nervous impulse traversing such a bifurcating fibre must pass equally to the main sensory nucleus and to the nucleus of the spinal tract and since it seems certain that pain has no representation in the main sensory nucleus these observations are difficult to interpret. Gerard suggested that pain is mediated by the fine non-medullated fibres which pass without bifurcation into the spinal tract. However, Windle's studies showed that many of the fine non-medullated fibres do bifurcate. The purely anatomical evidence is thus rather equivocal.

From the cases of Sjöqvist it can be affirmed that a lesion of the spinal tract causing analgesia and thermanæsthesia is compatible with normal tactile sensibility. Occasionally some degree of tactile hypoæsthesia (but never anæsthesia) is reported where analgesia has resulted from a lesion which has been proved to be confined to the medulla oblongata.

The central trigeminal or quintothalamic pathway.—Despite much careful investigation in the past on the anatomy of the central trigeminal pathway the accounts given in most modern anatomical and neurological writings are inadequate.

Hösel (1892) studied the brain of a woman, aged 52, who had suffered in earliest childhood a softening in the post-central region of one hemisphere. He found in the brain stem widespread degeneration of contralateral afferent tracts and sensory nuclei. The main sensory trigeminal nucleus was completely atrophied and there was atrophy in a small bundle of fibres in the pons lying between the ventral extremity of the superior cerebellar peduncle and the mesencephalic tract of the trigeminal nerve. As will be seen later the position of these atrophic fibres corresponds fairly closely with the dorsal quintothalamic tract of Wallenberg. Van Oordt (1896) examined the brain stem in a case where there was a softening in the medulla oblongata of some three months' duration. He was unable to trace any Wallerian degeneration but, from a study of the extent of the area of softening taken in conjunction with the clinical findings, he conjectured that the quintothalamic fibres crossed the raphe and ascended in the formatio reticularis of the opposite side.

Cajal (1895) was the first to give precise information on the position of the quintothalamic tract from the study of Golgi preparations in rabbits. He described two distinct quintothalamic tracts: (i) *a ventral tract,* consisting of crossed fibres, taking origin in the ganglion cells of the spinal nucleus and passing to the medial lemniscus of the opposite side, and (ii) *a dorsal tract,* consisting of uncrossed fibres, lying in the dorsolateral region of the formatio reticularis. Cajal later considerably modified this account of the quintothalamic tracts and his final views will be considered presently.

Wallenberg (1896), as already mentioned, placed lesions at various levels of the spinal tract of rabbits and studied the resulting Wallerian degeneration. He found that, following a destructive lesion in any part of the spinal tract and nucleus, degenerated fibres passed into the formatio reticularis of the opposite side just ventral to the hypoglossal nuclei. Traversing the substantia alba (in the region of the medial longitudinal bundles) they passed onwards to the formatio reticularis. Here they turned cephalad and ascended as a distinct tract to their termination in the ventral nucleus of the thalamus. As they were about to enter the thalamus they became blended with the fibres of the medial lemniscus. He also observed degeneration in the ipsilateral internal arcuate fibres and in the contralateral medial lemniscus, but this he attributed to coincident damage to the cuneate nucleus. In 1900 he made further and more extensive studies. In addition to confirming his former observation on the dorsal quintothalamic tract he traced numerous degenerated fibres into the ventral part of the opposite medial lemniscus. He was unable to find any evidence of a dorsal quintothalamic tract if the lesion lay caudal to the cephalad limit of the decussation of the pyramids, but he admitted that there was a possibility of the presence of a ventral quintothalamic tract such as Cajal had described. However, he believed that the great majority of the degenerated fibres which passed in the internal arcuate fibres to the opposite medial lemniscus arose in the gracile and cuneate nuclei or, alternatively, that they represented ascending fibres in the postero-lateral tract which had originated in the upper cervical segments of the spinal cord. Cajal (1900) returned to the subject; described a short quintothalamic tract composed of both crossed and uncrossed fibres in the dorsal region of the formatio reticularis and suggested that its function was solely related to reflex medullary functions. He adopted this view because of the close association of this short tract with the nuclei of the facial, glossopharyngeal, vagal and hypoglossal nerves.

Van Gehuchten (1901) made further experimental studies on rabbits, and his method followed that which Wallenberg had used. He was careful to localize the lesions in the spinal tract and nucleus both above and below the cephalad limit of the decussation of the pyramids. He concluded that when the lesion involved the nucleus of the spinal tract below the cephalad limit of the decussation of the pyramids degeneration resulted in the ipsilateral internal arcuate fibres and in the contralateral medial lemniscus and, further, that degeneration did not occur in the formatio reticularis of the same or opposite side. If, on the other hand, the spinal nucleus were involved cephalad to the level of the decussation of the pyramids, fibre degeneration could be followed into the dorsal part of the formatio reticularis of the opposite side. Within the medulla oblongata the fila of the hypoglossal nerve divided this dorsal quintothalamic tract into two distinct bundles but, in the pons, the tract became compact and united and also moved laterally so that it lay within the curve of the emerging fibres of the facial nerve. In the mid-brain this dorsal quintothalamic tract lay dorsolateral to the medial longitudinal bundle and close to the junction of the formatio reticularis with the central grey matter. Finally, it passed into the ventral nucleus of the thalamus by way of the internal medullary lamina. Throughout its entire extent it was completely independent of the medial lemniscus. The only point of difference between Wallenberg and Van Gehuchten concerned the existence of a ventral quintothalamic tract, but it would appear that Van Gehuchten's views later underwent a change for, in the account of the trigeminal nerve in his textbook of nervous diseases, he (1906) described only a dorsal quintothalamic tract and made no mention at all of a ventral quintothalamic tract.

The foregoing summary of the quintothalamic tracts has been concerned almost entirely with observations drawn from experimental studies. What little information exists of the actual course of the quintothalamic tract in man concerns almost exclusively the central connections of the main sensory nucleus. Indeed in regard to that part of the quintothalamic tract which originates in the spinal nucleus there is, if we except the rather vague suggestions of Hösel and van Oordt, only one case which gives any accurate information and this was the case of occlusion by embolism of the left posterior inferior cerebellar artery from which Wallenberg (1895) had first deduced the segmental representation of the spinal tract of the trigeminal nerve. After some years this patient died and Wallenberg (1901) made an anatomical examination of the brain stem and confirmed the clinical diagnosis made six years before. The focus of old softening, which was some 5 mm. long, lay in the lateral part of the medulla oblongata and at the level of the opening of the central canal. Weigert preparations showed that the quintothalamic tract pursued the same course in man as in the rabbit; that is, it occupied the dorsal part of the formatio reticularis on the side opposite to the lesion. The value of this observation is doubtful. It has never been claimed that the quintothalamic tract is large and prominent and there must surely be some difficulty in its recognition in a " negative " stain such as Weigert's.

From this period onwards direct experimental and clinical reports on the anatomy of the quintothalamic tract are lacking. As will presently be seen this period marks a change in the conception of the anatomy of the quintothalamic pathway. Dejerine (1914) summarized the divergent opinions on the quintothalamic tract but he made one important modification. He stated that the bulbar portion of the ventral tract crossed to the *retro-olivary* region of the opposite side. This should be compared with the statements by Cajal and van Gehuchten that the ventral quintothalamic tract crossed the raphe near its ventral extremity and joined the medial lemniscus in the *inter-olivary* region.

Spiller (1908) had originally accepted Wallenberg's views on the position of the quintothalamic tract but, in a later publication (1915), he stated: "The central tract of the trigeminal nerve in the medulla oblongata is believed by some to be situated a little in front of the hypoglossus nucleus; but it seems improbable that the fibres of temperature and pain from the face should occupy a tract distinct from that which contains the similar fibres from the trunk and limbs." In support of this opinion he cited Head and Holmes (1911) but these observers did not state precisely where the quintothalamic fibres joined with the main afferent tract for pain and temperature. From this time onwards, those who have mentioned the quintothalamic tract have all assumed that it lay in, or in close association with the spinothalamic tract. Stopford (1924) figured it in a position just medial to the spinothalamic tract and stated that there was ample evidence for assuming that the fibres taking origin in the spinal nucleus crossed the midline and formed a tract in the retro-olivary region and in close association with the spinothalamic tract.

It is probable that another factor has been effective in suggesting an anatomical association between the quintothalamic and spinothalamic tracts. This was the occasional occurrence of sensory loss on the contralateral face in cases of supposed posterior inferior cerebellar arterial occlusion. Now Stopford (1916) had shown that the substantia alba was not nourished by the posterior inferior cerebellar artery. Hence if the quintothalamic tract lay within the medial lemniscus, contralateral sensory loss on the face would not occur. Moreover, the assumption that the quintothalamic tract lay just medial to the spinothalamic tract received support from the frequent occurrence in cases of occlusion of the posterior inferior cerebellar artery of relative or absolute preservation of sensibility in the contralateral cervical region. Gordinier (1911) regarded the presence of a region of "cervical escape" as characteristic of the syndrome and argued that it resulted from the fact that the fibres conveying impulses for pain and temperature from the neck lay medial in the spinothalamic tract. Thus, if any part of the retro-olivary region escaped the ischæmic process, it was most likely to be that deep portion which contained the medial part of the spinothalamic tract, and the quintothalamic fibres, supposing them to lie most medial, would ordinarily escape destruction. It is obvious that the interpretation of this contralateral sensory loss on the face must affect the position we attribute to the quintothalamic tract. This question will be further discussed at a later stage.

Winkler (1921), in his study of the anatomy of the trigeminal nerve in the rabbit, gave a comprehensive account of the quintothalamic tract, but as he modified and amplified Cajal's original views, it is advisable to summarize his observations. He recognized a ventral and a dorsal quintothalamic tract, both entirely crossed and, in contradistinction to van Gehuchten, he stated that the nucleus of the spinal tract gave origin to the ventral tract throughout its entire extent. He considered that, in the medulla oblongata at any rate, a small part of the dorsal quintothalamic tract lay within the substantia alba and medial to the fila of the hypoglossal nerve. In the pons this medial portion of the dorsal tract passed laterally to blend with the main part of the dorsal tract in the formatio reticularis. He found that the fibres destined to form the ventral quintothalamic tract were represented by the most ventrolateral of the internal arcuate fibres. They traversed the medial portion of the olivary nucleus and crossed the raphe in the interolivary region. Turning cephalad they ascended in the medial and ventral region of the medial lemniscus but, on reaching the pons, they became less compact. A fair number of these fibres passed towards the lateral part of the lemniscus. This suggested that the fibres of the ventral quintothalamic tract came, at length, into association with the spinothalamic tract. He believed that the ventral quintothalamic tract mediated pain and thermal impulses and, if his anatomical observations were correct, it follows that the pathway for pain and thermal sensibility from the face is not so anomalous, in a physiological sense, as would appear at first sight. Winkler found that the main sensory nucleus sent accessions of crossed fibres to both the dorsal and ventral quintothalamic tracts but the ventral tract received by far the larger addition. His observations on the short crossed and uncrossed reflex tracts, previously described only by Cajal, were complicated chiefly because he dealt at great length with the pathway for the corneal reflex. In rabbits he found that lesions in the caudal part of the spinal nucleus abolished the corneal reflex but only for a period of two or three weeks. In order to cause permanent loss of the corneal reflex he found it necessary to destroy the spinal tract in its most cephalad part. From this he deduced that, in the rabbit at any rate, there was a double afferent arc for the corneal reflex. Normally it would seem that the impulse travelled by way of the fibres of the ophthalmic nerve to the most caudal part of the spinal tract. From there it was relayed by the short reflex pathway to the nucleus of the facial nerve. However, there was in addition a second and much shorter afferent pathway open to the impulse but this more direct pathway was only used if the longer and more caudal pathway were closed.

Within more recent years no observations have been published bearing directly on the quintothalamic tract. A certain number of examples of vascular lesions of the brainstem (mostly reported as instances of occlusion of the posterior inferior cerebellar artery) have been described and these were reviewed by Sheehan and Smyth (1937) in reporting two cases of occlusion of the vertebral artery. In all the reports, if it was mentioned at all, it was assumed that impulses underlying pain and thermal sensibility from the face crossed to the spinothalamic tract of the opposite side. Not a single case permitted a proper study of the secondary degeneration.

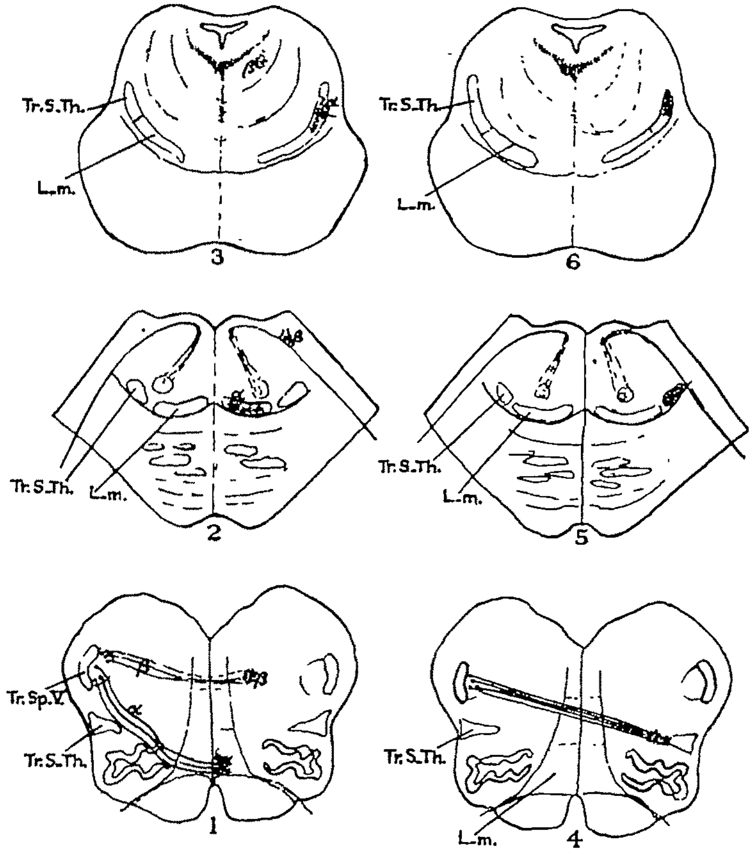

FIG. 1.—To illustrate the opposing views on the position of the quintothalamic tract. 1, 2, 3, the ventral and dorsal quintothalamic tracts according to Cajal, van Gehuchten and Winkler (Wallenberg recognized only the dorsal tract).

α the ventral quintothalamic tract.
β the dorsal quintothalamic tract.

4, 5, 6, the position of the quintothalamic tract according to Dejerine, Stopford, Elliot Smith and all recent English authors.

L.m.	Medial lemniscus.
Tr. Sp. V.	Spinal tract of the trigeminal nerve.
Tr. S. Th.	Spinothalamic tract.

From the preceding review it will be apparent that it is extremely difficult to convey a coherent account of the anatomical position and connections of the quintothalamic tracts since general agreement has never existed. The diagrams in fig. 1 give an outline of the most important hypotheses. Careful experimental and histological study carried out more than thirty years ago seems to point to the existence of two crossed quintothalamic tracts (Cajal, Wallenberg, van Gehuchten) and one short crossed and uncrossed tract solely concerned with bulbar and pontine reflexes (Cajal, Winkler).

DESCRIPTION OF CASES.

Case 1. Syringomyelia and Syringobulbia.—C. H. (116/37), a woman aged 66, was admitted to the National Hospital (Dr. E. A. Carmichael) on October 12 and died on October 28, 1937.

Some eight years previously she had fallen, striking the back of her head on the ground, and was shaken but not concussed. Three months later weakness of the right leg developed and, after a year, the right arm also became weak. During the next seven years the weakness slowly increased. For three or four years she had been unable to distinguish differences of temperature on her right arm and painless burns were sustained on numerous occasions. Her disabilities had increased rapidly in the year preceding admission to hospital. She walked with difficulty and the arms were almost powerless. Except for a slight precipitancy of micturition she made no complaints.

Examination.—Well-nourished elderly woman. Mentally alert and co-operative. Speech normal.

Cranial Nerves.—Visual acuity 6/18 right and left. Fields full on confrontation. Fundi appeared normal but were difficult to examine fully by reason of lenticular opacities. Hearing, taste and smell normal.

Pupils equal, but a little irregular in outline. Reaction to direct and consensual light and on convergence normal. Slow, coarse nystagmus to the left, and a fine rapid nystagmus to the right; neither were well sustained. External ocular movements full, no squint or diplopia. Slight right ptosis. Motor function of the 5th nerve normal. No abnormality of facial movements. The palatal reflexes very sluggish. Severe wasting of the trapezii. Tongue normal.

Sensation of the face (fig. 2).—All forms of sensation were entirely normal on the left half of the face. On the right, marked disturbances were present, but only in the territories of the ophthalmic and maxillary nerves. There was almost total loss for prick and temperature in the territory of the ophthalmic nerve and moderate hypoalgesia and slight loss of thermal sensibility in the territory of the maxillary nerve. The appreciation of cold appeared to be more deficient than that of heat. The right corneal reflex was diminished; the left was brisk. There was marked hypoalgesia on the right palate and faucial arch. Tactile sensibility was normal on the right half of the face.

Motor and sensory functions.—Weakness and wasting of the upper limbs were severe. The lower limbs were moderately spastic; the right more than the left. The tendon-jerks, except for the triceps-jerk, were absent in the upper limbs. The right knee and ankle jerks were exaggerated and the right plantar response was extensor.

Appreciation of prick and temperature was grossly impaired in the arms and chest and, on the right, tactile anæsthesia was superadded. On the left leg and trunk, to as high as the 6th intercostal space, there was moderate loss for prick and temperature.

Postural sensibility and discrimination of two points simultaneously applied were lost in the right upper limb but only slightly impaired in the right lower limb Examination of the other systems was negative.

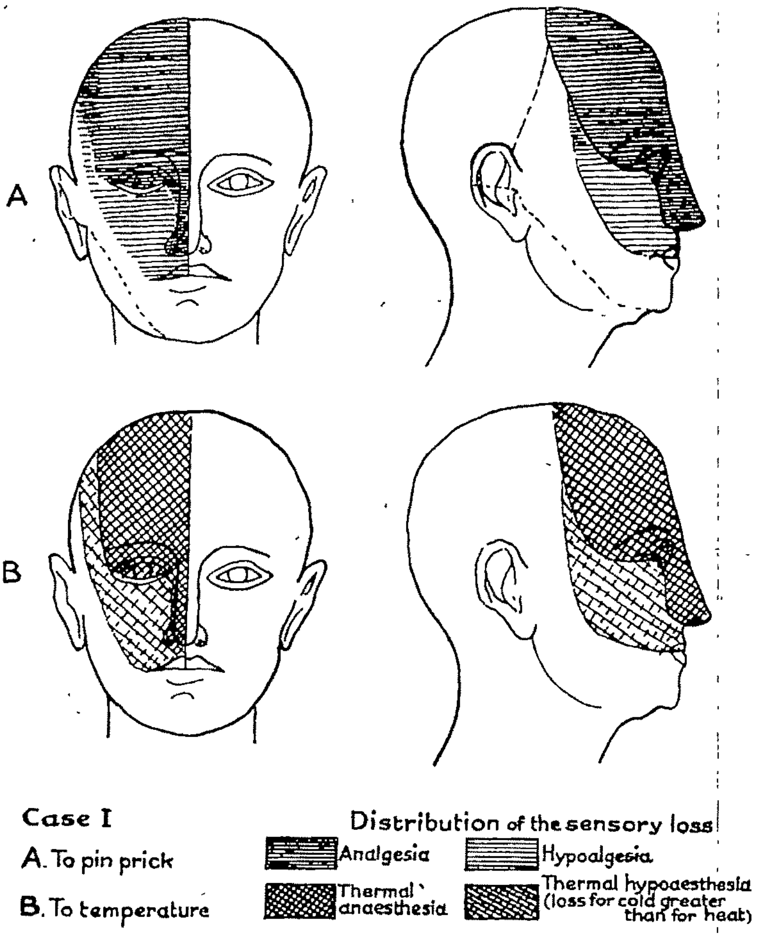
A
B
Case I
A. To pin prick
B. To temperature
Distribution of the sensory loss
Analgesia
Hypoalgesia
Thermal anaesthesia
Thermal hypoaesthesia (loss for cold greater than for heat)

FIG. 2.—Chart of the sensory disturbances on the face in Case 1. Note the strict limitation of analgesia and thermanæsthesia to the entire territory of the right ophthalmic nerve. The area of partial sensory loss was equally limited within the territory of the right maxillary nerve.

The cerebrospinal fluid was under an initial pressure of 150 mm. of water and there was no evidence of spinal block. The fluid contained nine lymphocytes per c.c. and 0·100 grms. per cent. of protein. The Wassermann reaction was negative in blood and fluid.

To exclude the possibility of an intramedullary high cervical tumour 0 5 c.c. of lipiodol was injected into the cisterna magna on October 26. There were no immediate untoward results but twelve hours later she became speechless and unable to swallow. Examination did not disclose any gross alteration in the physical signs previously noted. Death occurred some 48 hours after the cisternal injection.

Post-mortem examination (Dr. J G. Greenfield) within 12 hours of death. The convolutions of brain were atrophied, but the arteries at the base appeared normal (no thrombosis of vertebral or posterior inferior cerebellar arteries). The only other abnormality noted in the brain was a loss of bulk on the right side of the medulla oblongata at the level of the olivary nuclei The cord, throughout the cervical and dorsal part, was the seat of a smoothly-lined syringomyelic cavity which occupied its centre, but in the thoracic region, from the 3rd to the 11th thoracic segments, reached the surface along the left posterior grey column At the 12th thoracic segment it had shrunk to a small cavity in the grey matter on the left side of the cord. The posterior roots appeared rather more grey than normal.

Histological examination.—The medulla oblongata, pons and mid-brain were removed and cut into segments which were numbered in order so as to allow subsequent accurate reconstruction. After hardening in Weigert's primary mordant the blocks were embedded in celloidin. Serial sections were cut at 30 microns and every tenth section was stained by a modification of the Pal-Kultchitsky method and counterstained with alum-carmine. This procedure excluded an accurate estimation of the quality and degree of the gliosis and of minute cell changes but permitted thorough investigation of fibre tracts. The sections were mounted and numbered in ascending order from the junction of the cervical cord and medulla oblongata. It will suffice to describe in detail the sections of the brain-stem and of the first and second cervical segments.

At the second cervical segment the central grey matter was almost completely excavated. Only the tips of the anterior horns remained intact. The posterior grey columns and substantiæ gelatinosæ were completely destroyed by the syringomyelic process which, at this level, came to the periphery. The walls of the cavity were formed by dense glial tissue but the anterior white commissure was intact. The central canal was easily identified and appeared perfectly normal Small vessels (arterioles) were numerous in the glial tissue which formed the wall of the cavity All showed moderate adventitial thickening and, in a few, marked hyaline degeneration was present. There was pallor of the right lateral white column in the region of the pyramidal tract.

At the first cervical segment the cavity was smaller. On the left the substantia gelatinosa and spinal tract of the trigeminal nerve appeared normal On the right the cavity extended to the periphery in the region of the posterior grey column. The spinal tract of the trigeminal nerve and the substantia gelatinosa were destroyed. The posterior white columns were normal except for the presence of gliosis in their deeper parts.

At the level of the decussation of the pyramids (fig. 3) (Sections 1 to 4), the cavity was smaller and almost limited to the right half of the oblongata. The central canal was preserved, although embedded in glial tissue and seemingly within the cavity. On the right the cavity extended to the periphery and destroyed entirely the spinal nucleus of the trigeminal nerve. At the dorsal lip of the cavity a small part of the spinal tract of the trigeminal nerve could be identified. A few transversely cut fibres, lying ventral to the ventral lip of the cavity, appeared to represent the posterior spinocerebellar tract.

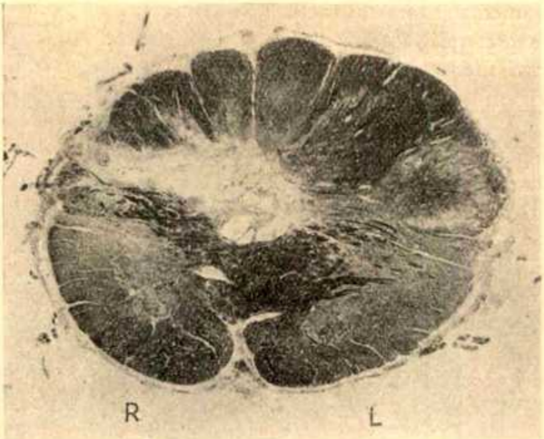

FIG. 3. *Case 1.*—Section at the level of the decussation of the pyramids. The cavity is limited to the right half of the medulla oblongata. The nucleus and spinal tract of the trigeminal nerve are destroyed and the right crossed pyramidal tract is partially invaded by gliosis. The fibres lying just ventral to the lateral extremity of the cavity probably represent the spinocerebellar tracts. Note the central canal lying within the cavity. Pal-Kultchitsky. × 5·5.

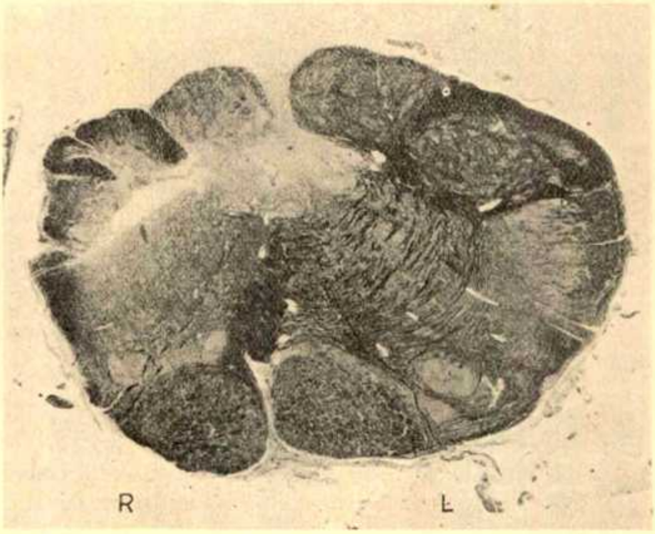

FIG. 4. *Case 1.*—Section (serial number 15) at the caudal level of the sensory decussation. The cavity has destroyed the nucleus of the spinal tract. The spinal tract itself is present but much reduced in bulk and unduly pale. There is a complete absence of internal arcuate fibres on this side and, on the opposite side (left), the medial lemniscus is wanting. There is slight pallor of the left pyramid. Pal-Kultchitsky. × 5·5.

At the level of the caudal extremity of the sensory decussation (fig. 4, Sections 9 to 15), the cavity assumed the form of a cleft extending from a point just dorsal to the central canal, ventrolaterally towards the spinal tract of the trigeminal nerve. The lateral extremity of the cavity had caused complete disorganization of the spinal nucleus of the trigeminal nerve and it reached the periphery immediately ventral to the spinal tract. The spinal tract was easily identified but it was much smaller than normal and pathologically pale. The gliosis surrounding the cavity was much less extensive than at more caudal levels. The nuclei of the posterior white columns were well developed and, on the left, heavily myelinated internal arcuate fibres swept ventromedially towards the raphe. On the right, by contrast, internal arcuate fibres were absent. The cavitation and associated gliosis had led to a marked reduction in the bulk of the right half of the medulla oblongata. There was considerable pallor (retrograde degeneration) of the left pyramidal tract, readily accounted for by the implication of the right crossed pyramidal tract in the syringomyelic process.

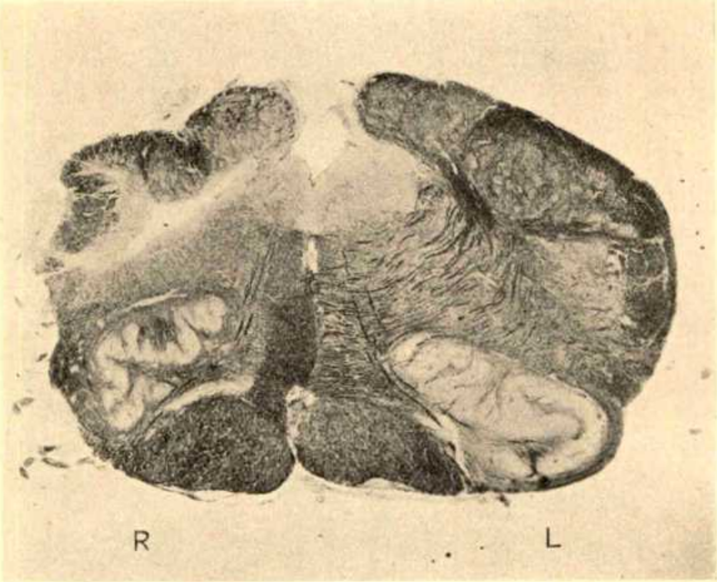

FIG. 5. *Case 1.*—Section (serial number 19) immediately caudal to the opening of the 4th ventricle. The cavity occupies a characteristic position. Medially it opens into the central canal dorsal to the dorsal vagal nucleus and laterally it touches the periphery ventral to the spinal tract of the trigeminal nerve. The nucleus of the spinal tract is destroyed by gliosis. Internal arcuate fibres are lacking on this side and, on the left, the medial lemniscus is wanting. There is a slight pallor of the left pyramid (retrograde degeneration). Note the shrinkage of the right half of the medulla oblongata. Pal-Kultchitsky. × 5·5.

At the cephalad extremity of the sensory decussation (fig. 5, Sections 16 to 21).—At Section 17 the central canal was nearing its termination and the olivary nuclei were well developed. The cavity was unchanged in shape. The spinal tract of the trigeminal nerve showed marked pallor and was still greatly reduced in bulk. The nucleus of the spinal tract was completely disorganized. The nuclei of the posterior white columns were less in evidence and the descending root of the vestibular nerve was well defined. The tractus solitarius was well seen on the left, but on the right no trace of it was apparent. Internal arcuate fibres were a striking feature on the left as they swept in bold curves towards the opposite medial lemniscus. On the right internal arcuate fibres were absent and, in consequence, there was no trace of the left medial lemniscus. The medial longitudinal bundles and tectospinal tracts appeared normal. The hypoglossal and dorsal vagal nuclei were intact. The pyramidal tracts appeared normal.

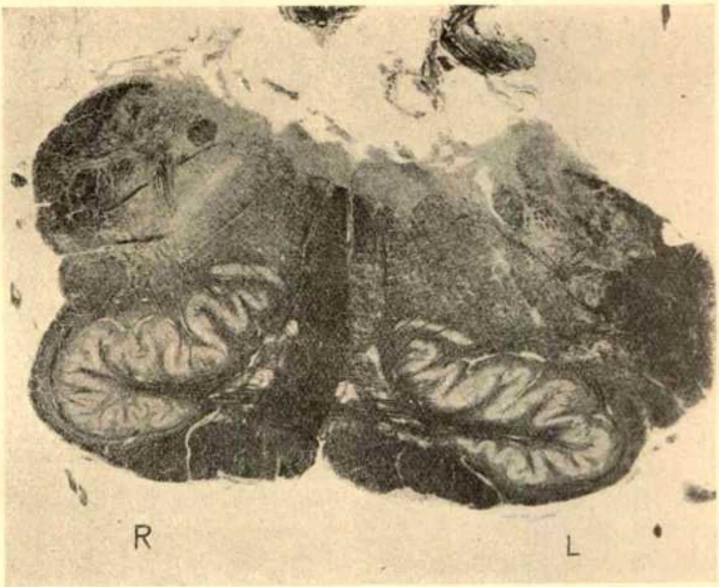

FIG. 6. *Case I.*—Section (serial number 32) cephalad to the opening of the central canal. On the right the cavity is reduced to a mere slit and, for the first time, internal arcuate fibres can be seen traversing the formatio reticularis. Of the nuclei of the posterior white columns only the cuneate remains and even it is difficult to define. The descending vestibular root is prominent. A small cleft medial to the left tractus solitarius is present here and in a few adjacent sections. It probably represents a true syringobulbar process but does not appear to have had any clinical significance. Pal-Kultchitsky. × 5·5.

At Section 24 the central canal had opened into the 4th ventricle. The only important change in the syringomyelic process was a marked reduction in the extent of the cavity. Medially it opened into the 4th ventricle (at a point just dorsal to the dorsal vagal nucleus) but laterally it did not reach the periphery. Its lateral extremity fell within the nucleus of the spinal tract of the trigeminal nerve. The nucleus of the spinal tract was still much disorganized by gliosis but the spinal tract itself was merely reduced in bulk and abnormally pale. No internal arcuate fibres could be identified on the right but it is conceivable that a few might have found their way into the formatio reticularis by insinuation around the lateral extremity of the cavity. The gracile nucleus had almost ended and the cuneate nucleus was small and poorly delimited.

At Section 31 the cavity was greatly reduced in size and took the form of a narrow cleft lying in the plane of the emerging fibres of the glossopharyngeal nerve. Neither extremity came to the periphery and the surrounding gliosis (as judged by pallor) was small. The right spinal tract and nucleus of the trigeminal nerve appeared to be almost normal and it seemed as though fibres passed from the region of the nucleus towards the ventral part of the raphe crossing in their course the medial part of the olivary nucleus. The inferior cerebellar peduncles and the medial and spinal vestibular nuclei were well developed. It was impossible to distinguish the cuneate nucleus as a distinct structure. By Section 32 the cavity had further diminished in size and in the next section it had disappeared. In sections immediately cephalad to this level its former position was represented by a band of slight pallor in the plane of the glossopharyngeal and vagal nerve roots. The most cephalad level at which the cavity was encountered corresponded with the most cephalad portions of the cuneate nuclei (fig. 6).

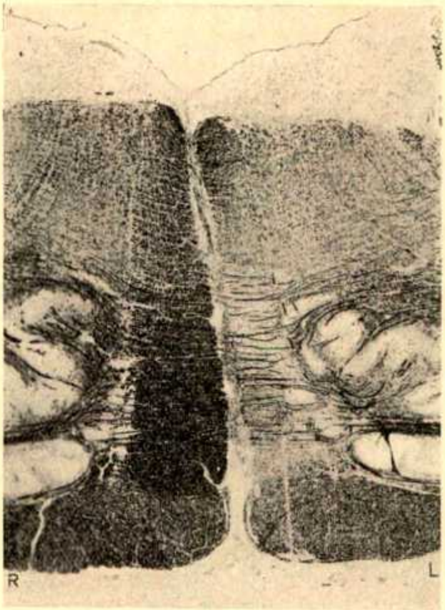

FIG. 7. *Case 1.*—Section (serial number 44) at the level of the cephalad half of the open part of the medulla oblongata. A fair number of ascending fibres are now evident, and, on the whole, they occupy the ventromedial region of the medial lemniscus. This section is far cephalad to the cavity and the appearances of the left medial lemniscus are in marked contrast with those seen in fig. 6. Pal-Kultchitsky. ×7·5.

Sections 33 to 59.—Throughout the cephalad half of the open portion of the medulla oblongata the fibre tracts and nuclear masses appeared normal excepting that the left medial lemniscus remained rudimentary. It was observed that, as the sections were traced cephalad, there was a progressive increase in the fibres in the left medial lemniscus (fig. 7). The probable source of these fibres will be discussed later, but for the present it should be noted that the nuclei of the posterior white columns had almost ended before the cavity had terminated. Consequently whatever the source of the progressively increasing fibres in the left medial lemniscus they clearly could not have originated as internal arcuate fibres from the nuclei of the posterior white columns, and for this reason their position and course merit close scrutiny. In the most caudal sections in which they could be certainly identified they occupied a narrow zone in the most ventral and medial part of the lemniscus and they were closely applied against the raphe. As the medulla oblongata was traced cephalad these fibres, as has been noted, increased in number but they continued to preserve their medial and ventral position. A few transversely cut fibres were, it is true, seen throughout the whole area of the left medial lemniscus, but the more definite and compact bundle in the ventromedial part stood out quite conspicuously at all levels of the medulla oblongata. In Sections 58 and 59, which corresponded with the junction of pons and medulla oblongata, the olivary nuclei became rapidly contracted and the right medial lemniscus expanded laterally. Simultaneously the fibres in the left medial lemniscus scattered although still maintaining their ventral position. This change was well seen in Section 62, where the site of the left lemniscus was evenly stippled with fibres. Lateral to this area of stippling lay the well-defined spinothalamic tract. Cephalad to the level of the facial nuclei the remnant of the left medial lemniscus underwent a further change. The fibres were still rather diffusely scattered but they seemed to be extending in a lateral direction and, at the level of the main sensory nucleus of the trigeminal nerve, it was impossible to distinguish them from the fibres of the spinothalamic tract. A close study of sections at this level gave the impression that the medial lemnisci received an accession of fibres at the level of, or immediately cephalad to, the main sensory nucleus of the trigeminal nerve. In the cephalad half of the pons and throughout the mid-brain the degenerated left medial lemniscus was easily followed. The right medial lemniscus was closely applied to the lateral margin of the red nucleus. In the corresponding region on the left side there was merely a rather diffuse pallor. In the most cephalad section in the series (at the level of the ventral nucleus of the thalamus) the picture was substantially similar but the pallor was too diffuse to allow of exact localization.

The Correlation of the Post-Mortem and Clinical Observations.

The motor and sensory signs in the trunk and limbs were such as are commonly found in syringomyelia. Over the chest and upper limbs the analgesia and thermanæsthesia could be attributed to the direct implication of the central grey matter of the spinal cord. The tactile anæsthesia on the right might be attributed to extension of cavitation into the right posterior grey columns so as to bring about destruction of the most medial fibres in the root entry zone. However, the virtual section of the posterior white columns on this side (by cavitation in the medulla oblongata), is perhaps more likely. The analgesia and thermanæsthesia on the left trunk and leg cannot be elucidated in this way for the cavitation did not extend into the lumbar segments of the spinal cord. They probably depended on some degree of involvement of the right spinothalamic tract. We know, indeed, that the right lateral column was affected, as evidenced by the spastic weakness of the right leg as well as by the retrograde pallor of the pyramidal tract. The weakness and wasting of the upper limbs were clearly secondary to partial destruction of the cells of the anterior grey columns in the cervical region of the spinal cord. In the medulla oblongata and pons the clinical signs were in accord with the histological changes seen. From above the level of the 2nd cervical segment of the spinal cord the cavity was limited to the right and it extended cephalad as high as the caudal part of the 4th ventricle. In its caudal half the cavity had caused a severe disorganization of the spinal tract of the trigeminal nerve and a complete destruction of the spinal nucleus. In its cephalad half the damage done by the cavity to the spinal tract and nucleus was less severe but at all levels, except those just caudal to the cephalad extremity of the cavity, the affection of the spinal nucleus was very definite. Furthermore, the cavity had effectively cut the path of all the internal arcuate fibres and, in consequence, the left medial lemniscus was absent.

The full interpretation of these observations, particularly in so far as they shed light on the segmental representation of the spinal tract of the trigeminal nerve, will be discussed more fully at a later stage. For the present the analgesia and thermanæsthesia in the territory of the right ophthalmic nerve will be attributed to the destruction of the most caudal part of the spinal tract of the trigeminal nerve. Similarly the hypoalgesia and thermal hypoæsthesia in the territory of the right maxillary nerve will be attributed to the *partial* destruction of the spinal tract of the trigeminal nerve in levels of the medulla oblongata towards the cephalad extremity of the cavitation.

The nystagmus, which is such a constant sign in syringobulbia is usually attributed to an affection of the descending root of the vestibular nerve, or of its central connections. This would be an adequate attribution in the present case.

Case 2.—Thrombotic occlusion of the right posterior inferior cerebellar artery.—A. B., a man aged 48, was admitted to a Leeds Hospital (Dr. Hugh Garland) on August 23 and died on September 4, 1936.

On August 19, 1936, the patient, who had previously enjoyed good health, was seized with sudden and severe giddiness, inability to swallow and loss of voice. In addition he complained of double vision and marked clumsiness in the use of his right arm and leg. When admitted to hospital four days after the onset of his illness he was drowsy and obviously gravely ill. Throughout his illness he was troubled by severe and persistent hiccup.

Examination.—The pupils were equal and regular in outline, their reactions were normal. There was diplopia (but no manifest strabismus) on looking down and particularly on looking to the right. There was coarse nystagmus on looking to the right and a more rapid and fine nystagmus to the left. There was no facial asymmetry or weakness. There was marked paresis of the right palate, the uvula being drawn up to the left on attempted phonation. There was aphonia and severe dysphagia. The function of taste was not examined.

Sensation on the face.—The following facts were established. There was a total analgesia on the right side of the face accurately confined to the territory of the trigeminal nerve. The right corneal reflex was absent. Thermal sensibility was not examined. There was an absence of any trace of sensory loss on the left half of the face and the left corneal reflex was active. Tactile sensibility was probably normal but as this observation was not recorded in writing it has not the validity of the other observations.

On the trunk and limbs there was a gross ataxy and hypotonia of the right arm and leg together with a slight degree of muscular weakness. The right plantar response was feebly extensor; the left was flexor. There was analgesia on the whole of the left half of the body excluding the territory of the left trigeminal nerve. The upper border of this sensory loss coincided with the posterior border of the trigeminal area. The patient died sixteen days after the onset of his symptoms.

Post-mortem examination was carried out by Dr. Polson of Leeds who found a thrombus occluding the right posterior inferior cerebellar artery. He very kindly preserved the brain-stem intact and sent it to the Pathological Laboratory of the National Hospital, Queen Square.

Histological examination.—Portions of the medulla oblongata and pons, after fixation in formol saline, were put into Weigert's primary mordant preliminary to the application of myelin sheath staining. Representative portions of the medulla oblongata and pons were reserved for examination by the Marchi technique. By these means sections were obtained from all levels of the medulla oblongata and pons and, though no attempt was made to secure strictly serial sections, there was little difficulty in forming an accurate estimation of the extent of the lesion and of the position of the Wallerian degeneration.

The nature and extent of the lesion.—The most caudal sections passed through the junction of medulla oblongata and cervical spinal cord at, approximately, the most caudal level of the decussation of the pyramids. In the first two sections the appearances were normal. By Section 3 it was apparent that the fibres of the right posterior spinocerebellar tract were abnormal. In cross section the myelin sheaths were vacuolated and reminiscent of the early changes seen in subacute combined degeneration of the cord and in certain cases of contusion of the cord. This appearance was of interest in that it suggested an anoxæmic effect on the nutrition of myelin, but the subject cannot be further pursued here. At the caudal level of the sensory decussation true ischæmic softening was first observed. It occupied a small area in the position of the posterior spinocerebellar and spinothalamic tracts. The spinal tract and nucleus of the trigeminal nerve were partially affected. Traced cephalad the lesion rapidly increased in size and at the opening of the central canal (fig. 8, Section 17) it assumed the form of an irregularly quadrilateral plate, and occupied the greater part of the right formatio reticularis. At this level it involved the cephalad portion of the gracile and cuneate nuclei, the anterior and posterior spinocerebellar tracts, the spinal tract and nucleus of the trigeminal nerve, the spinothalamic and rubrospinal tracts, the lateral half of the dorsal part of the olivary nucleus and the lateral half of the dorsal accessory olivary nucleus. The central grey matter, the descending root of the vestibular nerve, the medial lemniscus, the pyramidal tract, the medial and ventral parts of the olivary nucleus and a portion of the formatio reticularis adjacent to the substantia alba were all entirely spared. The dorsomedial tip of the area of softening touched, but did not invade, the tractus solitarius. In more cephalad sections the extent of the lesion remained fairly constant or, if anything, increased. At the mid-level of the open part of the medulla oblongata (Section 31) the lesion was beginning to diminish in size. The right inferior cerebellar peduncle and the spinal tract and nucleus of the trigeminal nerve were totally within the lesion. The whole of the olivary nucleus and the immediate retro-olivary region were now unaffected. In more cephalad sections the lesion grew rapidly smaller and just caudal to the uppermost fila of the glossopharyngeal nerve it occupied a small area corresponding to the position of the spinal tract of the trigeminal nerve (fig. 9, Section 34). More cephalad sections had not been stained by the Pal-Kultchitsky method but, from the Marchi preparations, it was evident that the most cephalad levels of the medulla oblongata were entirely free from softening. Sections stained by the Pal-Kultchitsky method, of all levels of the pons, showed a perfectly normal appearance. There was no trace of either ischæmic softening or secondary degeneration.

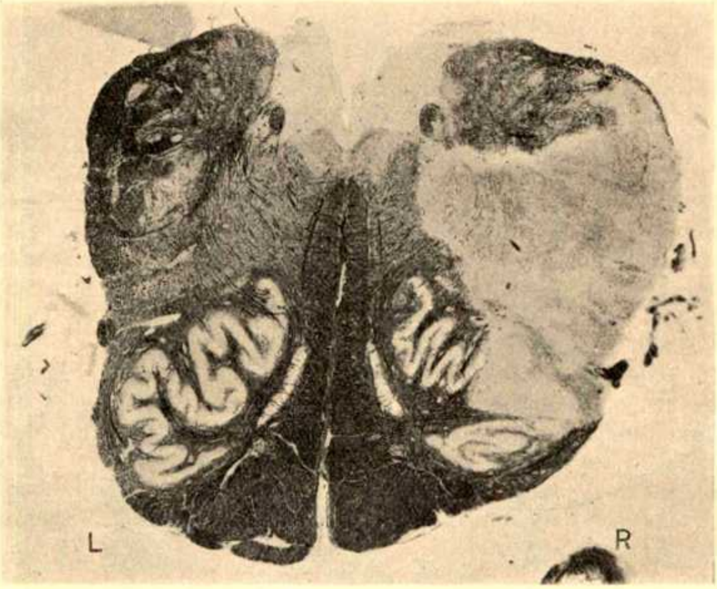

FIG. 8. *Case 2.*—Section immediately cephalad to the opening of the central canal. The focus of ischæmic softening occupies a large part of the right formatio reticularis and implicates the cuneate nucleus, the spinal nucleus and tract of the trigeminal nerve, the nucleus ambiguous, the spinocerebellar tracts, the spinothalamic tract and the lateral half of the dorsal part of the olivary nucleus. Pal-Kultchitsky. ×5·5.

The secondary degeneration of tracts demonstrated by the Marchi technique.—In sections passing through the caudal poles of the olivary nuclei the lesion was seen to occupy a wedge-shaped area interposed between the right olivary and cuneate nuclei. The softening partially implicated the spinal tract and nucleus of the trigeminal nerve. From the margin of the lesion degenerated fibres passed in broad curves towards the ventral half of the raphe. Many of these certainly took origin in the cells of the cuneate nucleus but it seemed probable that the most ventrolateral of these internal arcuate fibres originated in the neighbourhood of the nucleus of the spinal tract. Having crossed the raphe it was quite clear that these degenerated fibres were taking part in the formation of the medial lemniscus. The stippling in the left medial lemniscus thus produced was most dense in the ventral third of the substantia alba. Degenerated fibres were relatively scanty in the dorsal two-thirds of the lemniscus (fig. 10). It was noted as a fact of importance that there was a total absence of degeneration throughout the whole of the formatio reticularis of the left side of the medulla oblongata. In sections through the caudal half of the open part of the medulla oblongata the appearances confirmed and amplified the observations made at more caudal levels. The extent of the lesion was here at its maximum. The nuclei of the posterior white columns had almost ended but, on the right, a considerable number of degenerated internal arcuate fibres was still seen. The most ventrolateral of these fibres traversed the medial part of the olivary nucleus, crossed the raphe almost at right angles,

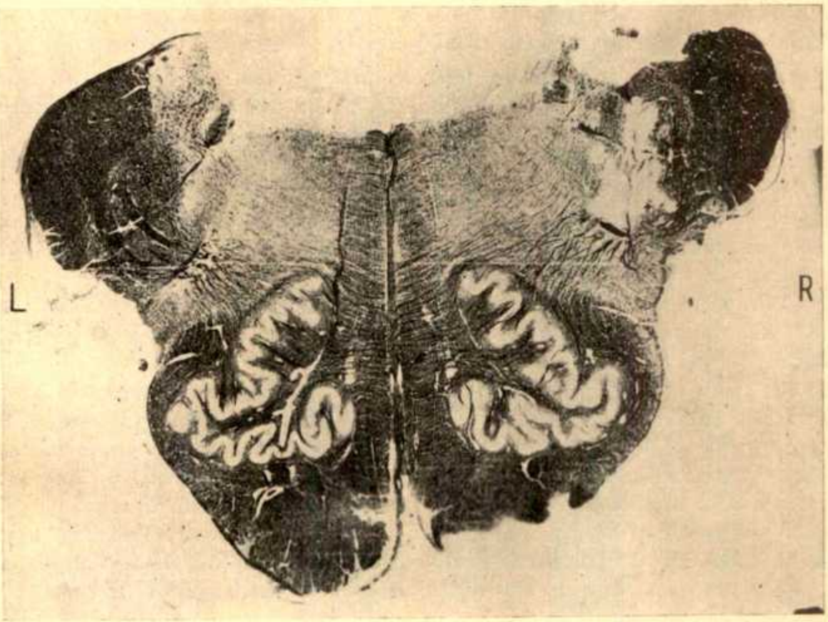

FIG. 9. *Case* 2.—Section close to the most cephalad level of the medulla oblongata. The focus of ischæmic softening in the right formatio reticularis has now contracted into a small area which occupies the position of nucleus of the spinal tract of the trigeminal nerve. Pal-Kultchitsky. × 5·5.

and finally joined the left medial lemniscus. The degeneration in the left medial lemniscus was by now very intense but it was limited to the ventral third of the substantia alba and, on the whole, it was most dense in the medial half of the lemniscus. Examination of the formatio reticularis on the left, and in particular of the region occupied by the spinothalamic tract, again showed a complete absence of secondary degeneration. This was equally true of the dorsomedial part of the left formatio reticularis, in which region Wallenberg had placed the dorsal quintothalamic tract. Two or three fine degenerated fibres were, it is true, seen in this region. Their significance will be referred to later. For the present it is sufficient to point out that they in no way approximated to a definite tract in the sense postulated by Wallenberg (fig. 11). In the most cephalad levels of the medulla oblongata the only abnormalities noted were :—

(1) Intense degeneration of the left medial lemniscus. The increased density of the degenerated fibres in the medial half of the lemniscus was still very apparent. At most a few degenerated fibres were seen scattered throughout the substantia alba, but this sparse degeneration was quantitatively equal on both sides.

(2) A moderately well-defined bundle of degenerated fibres immediately subjacent to the right antero-lateral sulcus. This certainly represented the ascending fibres of the spinothalamic tract which, at a more caudal level, had been involved in the focus of softening.

(3) Marked degeneration in the right interior cerebellar peduncle. This clearly followed on the implication of the posterior spinocerebellar tract in the focus of softening.

In the pons, at the level of the nuclei of the facial nerves, there was intense degeneration in the left medial lemniscus. On the right, the degenerated spinothalamic tract was easily identified. It formed a rather loose bundle of fibres lateral to the dorsal nucleus of the trapezoid body. In sections through the cephalad half of the pons the left medial lemniscus occupied a more lateral position and the degeneration was uniform throughout its substance. The degenerated right spinothalamic tract lay far laterally in the tegmentum and in close approximation to the ventrolateral convexity of the superior cerebellar peduncle.

THE CORRELATION OF THE POST MORTEM AND CLINICAL OBSERVATIONS.

This case is a typical example of the syndrome of occlusion of the posterior inferior cerebellar artery. The hypotonia and ataxy of the right arm and leg were attributable to destruction of the ipsilateral spinocerebellar tracts and by the scarcely less severe affection of the ipsilateral internal arcuate fibres. The contralateral analgesia on the trunk and limbs resulted from implication of the right spinothalamic tract. In this case the territory supplied by the posterior inferior cerebellar artery was maximum and the area of ischæmic softening extended into the formatio reticularis to the middle of the dorsal border of the olivary nucleus. The presence of an extensor plantar response on the right is perhaps rather difficult to account for. Possibly the right crossed pyramidal tract suffered some nutritional disturbance. That the right lateral white

PLATE II.

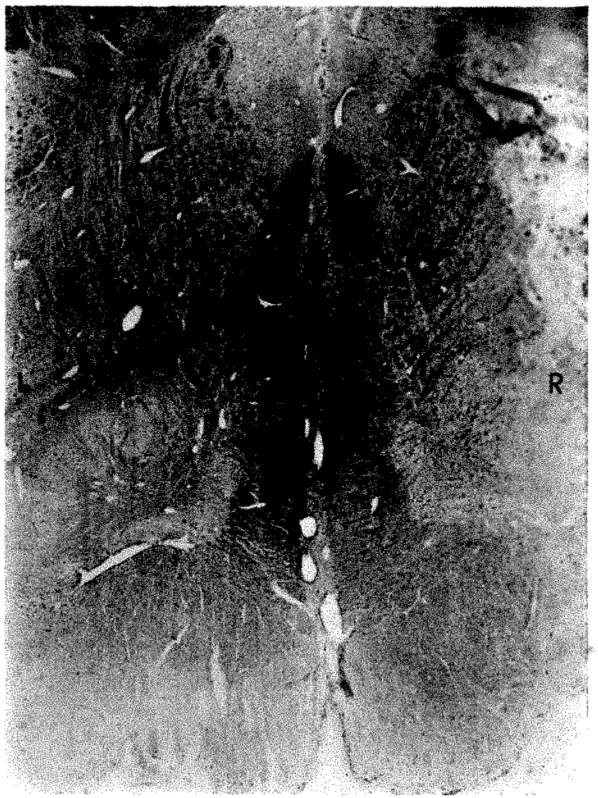

FIG. 10. *Case 2.*—Section towards the caudal part of the sensory decussation. Degenerated internal arcuate fibres pass from the region of the lesion towards the raphe. Ascending degenerated fibres are present in the opposite medial lemniscus. There is a complete absence of tract degeneration in the dorso-medial regions of the formatio reticularis. None of the degenerated fibres passes to the region of the spinothalamic tract. Marchi-Busch. × 8·5.

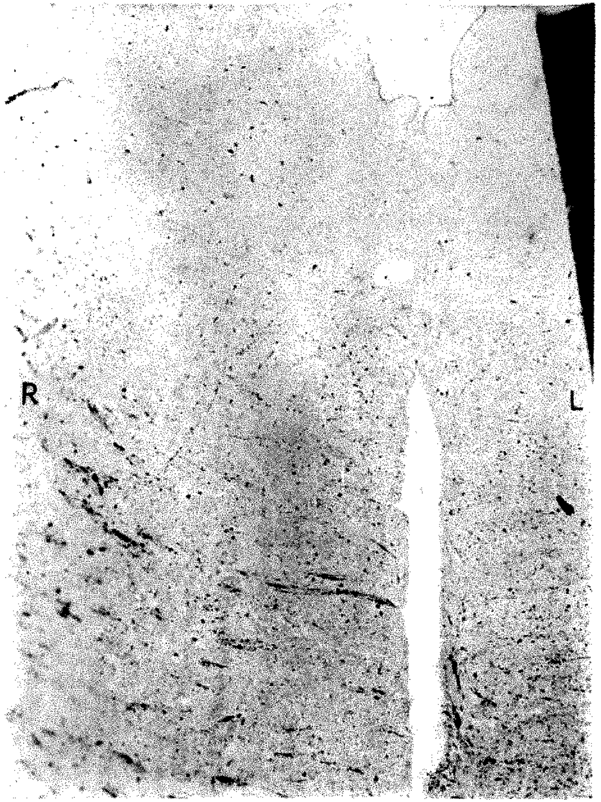

FIG. 11. *Case 2.*—Section at the level of the opening of the central canal. Towards the bottom of the plate the course of the degenerated internal arcuate fibres is well seen. Note the manner in which they bear ventralward after crossing the raphe. There is no evidence of a dorsal quintothalamic tract but a few fine degenerated fibres lying just ventrolateral to the position of the right hypoglossal nucleus occupy the position assigned to the reflex medullary pathway of the trigeminal nerve (Cajal). Marchi-Busch. × 26.

To illustrate article by **G. E.** *Smyth.*

column was affected was proved by the definite vacuolation observed in the region of the spinocerebellar tracts. The aphonia, dysphagia and right palatal palsy were explained by the destruction of the ipsilateral nucleus ambiguous. The causation of the nystagmus and diplopia is by no means clear. Both have frequently been reported in cases of this nature and in which the pons was intact. They probably result from an acute lesion which implicates the spinal vestibular tract or which cuts its connections with the medial longitudinal bundles. The chief interest in this case lies in the help that it affords in the localization of the quintothalamic tract and, in lesser degree, in an understanding of the segmental representation of the spinal tract and nucleus of the trigeminal nerve. For the present it is sufficient to reiterate that, neither caudally nor cephalad in the medulla oblongata, was there the least evidence of a dorsal quintothalamic tract or of an anatomical association of the spinothalamic and quintothalamic tracts.

Case 3.—Operative Section of the Spinal Tract of the Trigeminal Nerve for the Relief of Trigeminal Neuralgia.—C. D., a man, aged 39, was admitted to the National Hospital, Queen Square (Dr. E. A. Carmichael), on February 22, 1938. He complained of brief but extremely severe paroxysms of pain in the right upper lip and cheek which had occurred on and off for ten years. The history which he gave was typical of severe trigeminal neuralgia. The paroxysms had always been strictly confined within the territory of the right maxillary nerve. The usual exciting stimuli were all effective in provoking volleys of pain and, at the time of his admission, he was in a state of ketosis as a result of a fear of eating. In 1934, and again in 1936, alcohol injections had been made into the right trigeminal ganglion, but on each occasion he had only a few months' relief.

Examination.—In the territory of the right trigeminal nerve there was a very slight hypoalgesia; a residual effect of the alcohol injections. Other forms of sensibility were intact. The corneal reflexes were equal and brisk. Taste was normal. There was no other abnormality of the cranial nerves. Motor and sensory function were normal. The cardiovascular and respiratory systems were healthy. Radiograms of the skull showed changes suggestive of early Paget's Disease, the vault of the skull being particularly affected. Because of this it was felt that the temporal approach to the sensory root would be fraught with the risk of grave hæmorrhage and it was decided to attempt a section of the spinal tract. As a preliminary the state of sensibility in both trigeminal areas was carefully re-examined in order that there would be a proper standard for the assessment of the post-operative changes. Re-testing showed that apart from an extremely slight hypoalgesia in the whole of the right trigeminal area, trigeminal sensibility was normal. The lightest contacts with cotton wool were equally appreciated on both sides of the face. Two-point discrimination at a separation of 0·5 mm. was uniformly accurate on the lips and cheeks. The threshold for pressure pain was determined with the algometer. It was found that pressures of seven to nine pounds caused pain over the forehead, cheek and chin on both sides. Care was taken to ensure that the head was firmly supported whilst the pressure was applied.

Operation (Mr. Harvey Jackson), March 17, 1938.—The cerebellum and medulla oblongata were exposed by removing the overlying occipital bone and the arch of the atlas. The most caudal rootlet of the right vagus was taken as the guide and immediately caudal to this a horizontal incision was made with a guarded tenotomy knife into the lateral aspect of the oblongata to a depth of 3·5 mm. The knife, was inserted ventrally and drawn backwards till it emerged just ventral to the inferior cerebellar peduncle. Later the same day a cursory examination showed that there was analgesia of the right ophthalmic and maxillary territories with abolition of the right corneal reflex. Touch was unaffected. The general condition was satisfactory. Convalescence was uneventful. At no time was there any indication of severe cerebellar disturbance or of sensory disturbance on the trunk or limbs.

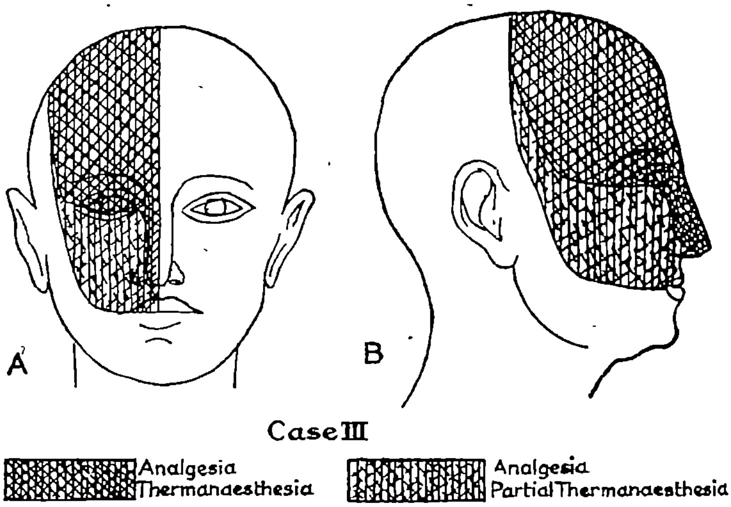
A
B
Case III
Analgesia Thermanaesthesia
Analgesia Partial Thermanaesthesia

FIG. 12.—Distribution of sensory loss in the territories of the right ophthalmic and maxillary nerves.

Post-operative condition on March 31, 1938.—At rest in bed the only trace of cerebellar disturbance was a relative slowness of alternating movements of the right arm and leg. However, the gait was definitely abnormal The patient veered towards the right and was slow and clumsy in turning. Apart from these signs the only abnormalities present were those referable to the right trigeminal nerve. The functions of the left trigeminal nerve were entirely normal. The diagrams (fig. 12) indicate the sensory loss. Analgesia was complete in the territories of the ophthalmic and maxillary nerves and the corneal reflex was absent The loss of thermal sensibility was complete in the area of the ophthalmic nerve and all temperatures evoked a neutral sensation. Over the territory of the maxillary nerve thermal discrimination was merely blunted. Slight inequalities in temperature were confused. Hot and cold were equally less well perceived. The inner aspect of the upper lip, the right half of the palate and the right faucial arch were analgesic. Taste and common sensation on the tongue were unaffected. *Pressure pain* was absent on the right forehead and cheek provided the head was firmly supported.

Whereas on the corresponding points on the left side the threshold for pain was from 7 to 9 pounds, on the right pressure of 20 pounds failed to arouse discomfort or pain. In testing for pressure pain in the cheek the examiner's finger was inserted into the patient's mouth to make counter pressure and to exclude deformation of the tissues by the thrust of the algometer. *Touch* was perfectly intact over the analgesic areas. Contacts with a von Frey's hair (2 grammes per sq. mm.) were equally well perceived on the two sides of the face. The patient himself stated that touching the analgesic areas aroused no sensation of tickle. *Discrimination of two points* simultaneously applied was as good on the analgesic area as on the sound side. A separation of 0·5 cm. was correctly perceived on both sides of the upper lip and along the sides of the nose. His symptoms were entirely relieved and there was a complete absence of subjective numbness and paræsthesia. This was in marked contrast with the state of many patients following section of the sensory root of the trigeminal nerve. It is interesting to note that headache, which lasted for about a week after the operation, was strictly confined to the left half of the scalp. This fact was spontaneously remarked on by the patient.

SUMMARY.

Operative section of the spinal tract of the trigeminal nerve at the level of the most caudal rootlet of the vagus was successfully performed without injury to the spinothalamic tract and with only (presumably) slight damage to the inferior cerebellar peduncle. There resulted an analgesia in the territories of the ipsilateral ophthalmic and maxillary nerves and loss of the corneal reflex. Thermal sensibility was lost over the ophthalmic territory and blunted over the territory of the maxillary nerve. Pressure pain was abolished on the analgesic side on the forehead, over the maxilla and on the cheek. Touch and discrimination of two points simultaneously applied were entirely unaffected.

DISCUSSION OF RESULTS.

Before any conclusions can be drawn from the cases whose clinical histories and pathological findings have just been recorded it is necessary to show that the cases were intrinsically suitable for study and that the pathological examinations were sufficiently full. The first patient (Case 1) was repeatedly examined by independent observers and the observations recorded were those, and only those, on which there was general agreement. It was unfortunate that deep sensibility of the face in two of the patients was not examined, but this omission in no way invalidates the assessment of other forms of sensibility. It is also regrettable that in Case 2 tactile and thermal sensibility were not accurately determined, but it will be proper to use this case to explain the distribution of the analgesia and the probable pathway of the bulbar portion of the quintothalamic tract.

With regard to the intrinsic suitability of the cases it will be conceded that, in the human subject, there are only two disease processes which should ordinarily be used for exact anatomical studies. The common systemic degenerations, infections and tumour formations are generally very poorly circumscribed. In contrast, syringobulbia and limited vascular lesions are much more sharply defined and in the past both have given information of great value. Of the two, circumscribed vascular lesions have, in the past, proved the more valuable, despite the objections which have been raised on the grounds that the initial disturbances following acute vascular lesions are necessarily in excess of what would have been expected from the extent of the lesion. This objection can be overcome, in great measure, if attention is confined to those disturbances which experience has shown to remain permanent and unaltered. Thus, in occlusion of the posterior inferior cerebellar artery it is commonly found that in the course of time the hemiataxy and disturbed sensibility in the trunk and limbs slowly recede or entirely disappear. It is otherwise with the trigeminal analgesia. A reference to the published case reports of patients surviving for years occlusion of the posterior inferior cerebellar artery shows that there is rarely any shrinkage of this analgesic area.

Syringobulbia may yield valuable information, but only in certain instances and when the histological examination has been thorough. It is certain that failure to satisfy these requirements is responsible in no small measure for the confusion which besets the problems presented by the trigeminal nerve. It must be evident that it is not possible to draw reliable conclusions from cases of syringobulbia in which the cavity is interrupted by bridges of normal tissue. The risk of error becomes even greater when the cavity destroys only a part of the spinal nucleus of the trigeminal nerve and when the interpretation of the distribution of the sensory loss is made to rest on the supposed interruption of the second sensory neurone.

The three cases here reported appear suitable for study. They presented clear-cut lesions and the histopathological studies were made at all levels throughout the extent of the lesions.

The segmental representation of the spinal tract and nucleus of the trigeminal nerve.—The material provided by these cases lends strong support to the view that the representation within the spinal tract and nucleus of the trigeminal nerve is in terms of the peripheral divisions of the nerve and in an order which is the inverse of the peripheral distribution. In Case 1 there was, during life, a well-defined sensory loss on the right side of the face. It is important to note that the medial border of the area of analgesia and thermal anæsthesia extended along the midline of the nose and from there passed upwards to the vertex. Reference to fig. 2 makes this clear and shows also the hypoalgesia and partial thermanæsthesia in the territory of the right maxillary nerve. The crucial observations in this case were the accurate correspondence of the areas of sensory loss within the territories of the ophthalmic and maxillary nerves and the sharp medial border of the area of sensory loss at the midline of the face. Furthermore, it should be noted that the sensory loss was most intense in the territory of the ophthalmic nerve and only partial in the territory of the maxillary nerve.

Pathologically a cavity was found in the right half of the caudal third of the medulla oblongata and destroying the more caudal part of the spinal tract and nucleus of the trigeminal nerve.

The clinical and histological observations in this case may be harmonized on the assumption that all the ophthalmic fibres descend to the most caudal part of the spinal tract of the trigeminal nerve and there end in synaptic relation with the most caudal part of the nucleus of the spinal tract. The maxillary fibres also descend in the spinal tract but they end in relation to an intermediate part of the nucleus of the spinal tract. The partial involvement of these maxillary fibres is in keeping with the partial nature of the sensory loss in the territory of the maxillary nerve and it is explicable by the incomplete nature of the lesion of the nucleus of the spinal tract towards the more cephalad extremity of the cavity. The complete escape of the mandibular fibres shows that they terminate within the nucleus of the spinal tract cephalad to the most cephalad limit of the cavity. The clinical and histological findings in Case 2 are in conformity with these views. Here there was a total analgesia strictly limited to the territory of the right trigeminal nerve. Histological examination showed that a focus of ischæmic softening had destroyed the spinal tract and its nucleus, but, in this instance, they were destroyed at a more cephalad level than in Case 1. Since it was plain that the most cephalad level of the medulla oblongata was quite unaffected by the lesion and it follows that the mandibular fibres must end in the nucleus of the spinal tract at some level between the opening of the central canal and the most cephalad level of the medulla oblongata. These limits are wide and there is nothing in either of these cases to indicate whether the mandibular fibres end diffusely throughout the very considerable length set by these limits or more discretely towards its caudal or cephalad limits. The results obtained by Sjöqvist (1938) appear to settle this problem and it appears highly probable that the mandibular fibres in the spinal tract end immediately caudal to the middle of the open part of the medulla oblongata.

It is important to note the distribution of the thermanæsthesia in Case 3. The area of total thermanæsthesia was strictly limited to the territory of the ophthalmic nerve. Similarly the area of partial thermanæsthesia was accurately confined to the territory of the maxillary nerve. However, analgesia was complete in the maxillary territory and this suggests that the segment of the nucleus of the spinal tract concerned with thermal sensibility lies at a level cephalad to that for pain. It is plain that the distribution and degree of the defect of thermal sensibility in this case can only be explained on the assumption that its representation in the spinal tract is in terms of the peripheral distribution of the nerve and that those fibres of the ophthalmic nerve, which mediate thermal impulses, descend further caudally than similar fibres from the maxillary nerve. As in Cases 1 and 2, the sensory disturbances in this case cannot be reconciled with a theory which postulates a segmental representation in the spinal tract in terms of concentric zones converging towards the nose and mouth.

Direct histological examination of the nucleus of the spinal tract of the trigeminal nerve cannot, of course, be expected to give much direct evidence bearing on the segmental representation of the spinal tract and nucleus. The significance of the variations in the morphology of the nucleus of the spinal tract of the trigeminal nerve is obscure but it is permissible to suspect that they subserve a functional differentiation. It may be that the fibres of all three components of the trigeminal nerve end in relation to that part of the nucleus of the spinal tract which lies in the caudal third of the medulla oblongata and whose structure is uniform with that of the substantia gelatinosa. Alternatively only the fibres of the ophthalmic and maxillary nerves may pass to this caudal portion of the nucleus, leaving the mandibular fibres to make synaptic relation with a part or the whole of the cephalad two-thirds of the nucleus of the spinal tract. Either hypothesis would be in harmony with the clinical and pathological findings in these cases but, on the whole, the second would appear the more reasonable and, furthermore, it is in agreement with Sjöqvist's observations.

At this point it is instructive to refer to the distribution of sensory loss on the face in the reported cases of the retro-olivary syndrome of vascular origin. Such a study throws further light on the probable nature of the segmental representation in the spinal tract and nucleus of the trigeminal nerve. In a recent paper Sheehan and Smyth (1937) reviewed all the examples of this syndrome published since Stopford's critical analysis in 1924. In three-quarters of the cases reviewed the trigeminal sensory loss was on the side of the lesion and in the great majority the analgesia affected all three branches of the trigeminal nerve but, when the sensory loss was less extensive, it was invariably greatest in the territory of the ophthalmic nerve or in the territories of the ophthalmic and maxillary nerves. Moreover, the sensory loss invariably extended to the mid-line of the face and was exclusively in terms of the three divisions of the trigeminal nerve. Where only a part of the trigeminal area was affected the territory of the ophthalmic nerve was the most likely to suffer, and, if any part of the trigeminal area escaped, then the mandibular territory was the area showing a state of normal sensibility. It has been shown that vascular lesions of the lateral area of the medulla oblongata, thanks to the variability in the vascular supply, may involve the spinal tract and nucleus of the trigeminal nerve at varying levels. Such lesions perform remarkably clear-cut experimental sections of the spinal tract and give thereby information of the greatest value. From the resulting sensory disturbances the conclusion is inescapable that the peripheral divisions of the trigeminal nerve are represented within the spinal tract in such a manner that the ophthalmic fibres terminate most caudally, the mandibular fibres most cephalad, whilst the maxillary fibres end at an intermediate level.

The evidence in favour of the contrary hypothesis, namely that the representation is in terms of concentric zones converging on the nose and mouth, must next be considered. This hypothesis, associated with the names of von Sölder, Schlesinger, Dejerine and Woods, has been formulated almost, if not quite, exclusively on observations in cases of syringobulbia. If not a few instances the cases cited as proving the correctness of this theory have lacked post-mortem confirmation. Von Sölder's paper was based entirely on clinical observation. Schlesinger in his great series of cases obtained post-mortem verification in many but too often the notes on the state of sensibility in the face were scanty or altogether absent. The reasons for adopting a critical attitude to Woods's conclusions have already been sufficiently stressed. It is not for one moment suggested that a distribution of sensory loss, such as formed the basis for this hypothesis, does not occur in syringobulbia. On the other hand by no means all cases of syringobulbia show trigeminal analgesia of concentric distribution and in this respect the conclusions of Jonesco-Sisesti, in his extensive series of cases, were contrary to the observations of earlier writers. The cases reported by Wyllie (1923) and by Taylor, Greenfield and Martin, all tend to show that the representation of the spinal tract is in terms of the peripheral divisions. Taylor, Greenfield and Martin's second patient was interesting because there developed, towards the end of her life, partial analgesia and slight tactile anæsthesia in the territory of the ophthalmic nerve in the previously unaffected side. The finding of even the slightest degree of tactile anæsthesia in a case of disease limited to the medulla oblongata will require explanation later. At present it is important to consider the possible cause of the analgesia on the side which had so long remained unaffected. Fortunately the slides of this case were available for further study. In the medulla oblongata there was a typical cavity in the dorsal part of the formatio reticularis. The cavity destroyed the spinal tract and nucleus of the left trigeminal nerve but its upper limit could not be precisely determined for the brain stem had not been sectioned in its entirety. Examination at the levels of the first cervical segment and caudal part of the decussation of the pyramids disclosed that the cavity had invaded and destroyed the spinal tract and substantia gelatinosa on both sides. The cavity had, in fact, destroyed the most caudal part of the spinal tract and nucleus of the left trigeminal nerve and it is clear that this lesion was responsible for the analgesia in the territory of the left ophthalmic nerve. Were the hypothesis of Von Sölder and Schlesinger true the patient would have presented a zone of analgesia anterior to the vertex-ear-chin line. And the fact that she did not is further evidence that the notion of a segmental representation in terms of concentric zones cannot be sustained.

The hypothesis that the peripheral divisions of the trigeminal nerve are represented in an inverse order in the spinal tract and nucleus is the only theory that is in harmony with the observations here recorded. Furthermore it is in harmony with experimental observations; with clinical observations in succinct vascular lesions and with the results of comparative anatomical studies.

The position of the quintothalamic tract within the medulla oblongata and pons.—The uncertainty existing on this subject has been sufficiently indicated in the historical survey. In Case 2, it will be remembered, there was a vascular softening, limited to the retro-olivary region of one side, and so placed that it had destroyed completely the spinal tract and nucleus of the trigeminal nerve between the levels of the most caudal plane of the sensory decussation and the most cephalad fila of the glossopharyngeus. The patient lived for some two weeks and the Marchi technique was successfully applied.

A consideration of the clinical and pathological observations in this case makes it hard to escape the conclusion that the quintothalamic tract, or, at any rate, that portion of it which originates in the cephalad three-quarters of the nucleus of the spinal tract, pursues its central course in company with the fibres of the opposite medial lemniscus. In this instance at least there is nothing in favour of the existence of a dorsal quintothalamic tract; nothing to suggest that the quintothalamic tract and spinothalamic tract are closely related in position, and only meagre evidence in favour of the existence of a short reflex central tract. It may fairly be objected that, since the lesion did not implicate the nucleus of the spinal tract at its caudal extremity, we are left in ignorance of the position of the quintothalamic pathway originating at this caudal level. This objection receives added force from the fact that the caudal extremity of the nucleus of the spinal tract is presumably related to the fibres of the ophthalmic nerve. Several factors, however, mitigate the force of this objection. In the first place the lesion implicated the nucleus of the spinal tract as low as the caudal planes of the sensory decussation. It is probable that some at any rate of the ophthalmic fibres end as far cephalad as this. Secondly it must be remembered that Cajal, Wallenberg and van Gehuchten all described fibres which passed to the ventral region of the opposite medial lemniscus when experimental lesions were situated in the most caudal levels of the medulla oblongata and, further, that they failed to find any tract of a dorsal quintothalamic tract at these caudal levels. Indeed, Wallenberg, who denied the existence of a ventral quintothalamic tract, was unable to find any trace of secondary ascending degeneration, other than in the opposite medial lemniscus, provided the lesion did not implicate the nucleus of the spinal tract cephalad to the opening of the central canal.

The hypothesis that a crossed ventral quintothalamic tract, within the system of the medial lemniscus, is the most important if not the only long central bulbar trigeminal tract is completely in accord with the clinical observations here recorded. In Case 2 sensibility on the left trigeminal field (the side contralateral to the lesion) was normal. From the crossed analgesia on the trunk and limbs it was quite certain that there was interruption of the right spinothalamic tract and examination of the medulla oblongata showed conclusively that the right retro-olivary region was extensively softened. The integrity of sensation on the left half of the face is easily comprehensible if it is assumed that the quintothalamic tract lies in the medial lemniscus, but it cannot be satisfactorily explained if it is assumed that the quintothalamic and spinothalamic are in close anatomical relation. The observations recorded in Case 1 give, by comparison, much less help. So far as they go they confirm the view that the bulbar portion of the quintothalamic tract passes cephalad in company with the fibres of the medial lemniscus. In this case it was noted that there was a total absence of the left medial lemniscus caudal to the cephalad extremity of the cavity. Cephalad to the cavity there was a progressive increase in the number of fibres in the left medial lemniscus. At first this increase could properly be attributed to an accession of fibres from the cephalad parts of the nuclei of the posterior white columns but cephalad to the termination of these nuclei it was clear that the bulk of the left medial lemniscus was increasing. It is difficult to assign a cause for this progressive increase unless one supposes that the fibres originate in the cephalad half of the nucleus of the spinal tract of the trigeminal nerve. As the fibres in the left medial lemniscus increased it was interesting to observe that they tended to take up a ventromedial position. A comparison of Sections 32 and 44 (figs. 6 and 7) shows clearly the difference in the left medial lemniscus caudal and cephalad to the cephalad extremity of the cavity. As the sections are traced cephalad through the pons the fibres in the left medial lemniscus undergo a further change. In caudal levels of the pons the fibres maintain a medial position within the region of the medial lemniscus but, just caudal to the main sensory nucleus of the trigeminal nerve, it is apparent that the fibres in the left medial lemniscus are becoming more scattered and, in general, they occupy a more lateral position. Cephalad to the level of the main sensory nucleus of the trigeminal nerve these fibres can no longer be distinctly identified and the appearances suggest strongly that they have merged with the fibres of the spinothalamic tract. If this interpretation is correct it follows that the quintothalamic tract in man follows a course very similar to that in the rabbit, for Winkler expressly stated that the ventral quintothalamic tract of the rabbit blended with the spinothalamic tract in the cephalad half of the pons.

A critical consideration of this hypothesis of the course of the quintothalamic tract shows that its adoption does no violence to those general principles which appear to govern the disposition of the great afferent tracts within the spinal cord and brain stem. On this hypothesis the fibres mediating painful and thermal impulses from the nucleus of the spinal tract of the trigeminal nerve use the course of the opposite medial lemniscus in order to attain the cephalad part of the pons. Ultimately, it would seem, they blend with the fibres of the spinothalamic tract and thereby all impulses underlying pain and thermal sensibility from one half of the body become grouped in one tract.

At this point it becomes necessary to make a detailed examination of certain clinical observations which, superficially, appear to negative the hypothesis that the quintothalamic tract and medial lemniscus are in close anatomical association.

Stopford (1916) has shown that the substantia alba is never nourished by the posterior inferior cerebellar artery and this observation is in full accord with the clinical findings in those cases of occlusion of the posterior inferior cerebellar artery where the trigeminal sensory loss is unilateral. A minority of the reported cases of this syndrome has, however, shown some degree of analgesia in the contralateral trigeminal territory and this demands explanation. In the instances of occlusion of the posterior inferior cerebellar artery reported up to 1937 contralateral trigeminal sensory loss was present in ten out of a total of forty-one cases. Included in these ten cases were five in which some degree of bilateral trigeminal sensory loss was present. The earlier workers were familiar with this occasional contralateral trigeminal sensory loss and Spiller (1908) referred it to implication of the quintothalamic tract. This was at a time when Spiller accepted (rather unwillingly) Wallenberg's dorsal tract as the principal quintothalamic tract. In a later publication Spiller (1915) abandoned his earlier view and adopted Dejerine's suggestion that the quintothalamic tract joined the spinothalamic tract in the retro-olivary region. This theory was also adopted by Head and Holmes (1912), by Stopford (1924, 1930), and in fact, by most English writers. In support of the localization of the quintothalamic tract in the retro-olivary region it has been suggested that the frequently observed cervical sparing implies a lamination of the spinothalamic tract and that the fibres from the cervical region probably take up a medial position in the tract. By extension it might be assumed that the fibres from the nucleus of the spinal tract of the trigeminal nerve would occupy a more medial position than those from the cervical region. However, this hypothesis, though at first sight attractive, was never fully satisfactory. In the great majority of cases of occlusion of the posterior inferior cerebellar artery coming to post-mortem examination the softening in the retro-olivary region was extensive (as in Case 2) and it is difficult to believe that any part of the spinothalamic tract could have escaped destruction. It has, indeed, been suggested that more thorough physical examination might have disclosed some degree of contralateral analgesia in many of the cases where in fact only ipsilateral trigeminal sensory loss was reported. Against this suggestion is the fact that most of the cases were reported by neurologists well aware of the possibility of the existence of contralateral trigeminal sensory defects. The resolution of this dilemma is admittedly difficult. It would be solved, however, if it could be shown with a reasonable degree of probability that contralateral trigeminal sensory loss does not in fact occur in true examples of occlusion of the posterior inferior cerebellar artery, but only in cases in which the softening implicates the caudal levels of the pontine tegmentum. That this may be the true explanation is by no means so improbable as might appear at first sight. The following considerations will be advanced in its support. It is now well known that it may be impossible to distinguish clinically between the syndromes of the posterior inferior cerebellar and vertebral arteries and, recently, Foix, Hillemand and Schalit (1925) and Foix and Hillemand (1925) have drawn attention to a further difficulty in the way of correct anatomical diagnosis. They believe that the importance of the posterior inferior cerebellar artery in the production of the retro-olivary syndrome has been exaggerated and that other arteries may be and often are responsible. Their opinion was based on a case clinically resembling occlusion of the posterior inferior cerebellar artery but which autopsy proved to be due to occlusion of a previously unnamed branch of the basilar artery. This vessel, termed by them *"l'artère de la fosette laterale du bulbe,"* is one of a pair of short circumferential arteries which arises close to the origin of the basilar artery and passes laterally to supply the retro-olivary region in the most cephalad levels of the medulla oblongata and the ventral part of the pontine tegmentum. They defined the territory of this artery by injecting the vessel in the cadaver. Foix and his fellow workers believed that many alleged examples of occlusion of the posterior inferior cerebellar artery were, in fact, examples of occlusion of the artery of the lateral medullary fossa. Of more immediate importance is the help this suggestion gives in explanation of contralateral trigeminal sensory loss in supposed occlusion of the posterior inferior cerebellar artery. An appeal to the nine reported examples of occlusion of the posterior inferior cerebellar artery in which there was sensory loss on the contralateral half of the face is, unfortunately, not very helpful, for in many of them the clinical and pathological details were scanty. Two of six cases reported by Merritt and Finland (1930) showed bilateral trigeminal sensory loss and in both these cases there was fairly clear evidence of a pontine lesion. This was shown by the presence of definite facial palsy, nerve deafness and frank abducens palsy. It is clear that signs such as these do not result from pure lesions of the medulla oblongata and consequently, as Stopford has proved, whatever the vessel occluded it could not have been the posterior inferior cerebellar artery. The case reported by Hall and Eaves (1934) under the title of "Posterior-Inferior Cerebellar Thrombosis with Unusual Features" is even more instructive. It concerned a man who died some four months after suffering a stroke which was characterized by severe vertigo and transient facial palsy. Examination disclosed severe loss for touch, prick and temperature on the right half of the body (including the face to as high as the level of the eyebrow). Sensibility on the left half of the body (including the face) was entirely normal. At autopsy a focus of old-standing softening was found in the left half of the medulla oblongata. The nucleus and spinal tract of the trigeminal nerve were, at most, only slightly involved by the lesion. The lesion, however, quite definitely extended cephalad into the ventral part of the left pontine tegmentum. Now it must be remarked that though the case was reported as an instance of posterior inferior cerebellar arterial thrombosis the actual condition of individual vessels was not mentioned. It was merely stated that the branches of the vertebral arteries showed diffuse arteriosclerosis. It follows from what has been said previously that there must be some doubt in accepting this case as an example of thrombosis of the posterior inferior cerebellar artery. As a matter of fact the plates figuring the lesion showed that the affected area bears a striking resemblance to the territory of the artery of the lateral medullary fossa as defined by Foix and his fellow workers. In connection with the problem at issue the essential fact that emerges from a study of Hall and Eaves's case is that a contralateral sensory loss in the territory of the trigeminal nerve was found in association with a vascular softening which certainly affected the ventral and medial parts of the pontine tegmentum. A lesion in this situation may very likely interfere with the function of the medial lemniscus. A somewhat similar case came under the notice of the writer and is worthy of brief mention despite the absence of post-mortem verification.

A single man, aged 38, was admitted to the National Hospital, Queen Square (Dr. Gordon Holmes), on October 10, 1936. Three weeks previous to admission he was attacked by sudden numbness and tingling of the right half of the body. For the next two weeks nothing further happened and then there developed diplopia with inability to look to the left, severe left-sided deafness, paralysis of the left face, severe dysphagia and a tendency to fall to the right. On examination the essential findings were—complete paralysis of conjugate movement of the eyes to the left and nystagmus and diplopia on looking to the right, the left pupil was smaller than the right, severe left facial paralysis, paralysis of the left palate and absence of the left palatal reflex. There was a combination of hypoalgesia with overaction to painful stimuli on the whole of the right half of the body (including the face). In the same area there was moderate tactile anæsthesia and a severe loss of postural discrimination in the right arm and leg. There was a mild degree of hypotonia and ataxia in the right limbs. The right plantar response was extensor. The patient made a slow recovery and one year after the onset of his symptoms the only remaining abnormalities were weakness of the left face and slight hypoalgesia on the whole of the right half of the body. The results of special investigations proved unhelpful but it was evident that he had sustained a vascular lesion of the caudal part of the left half of the pons.

Many similar cases have undoubtedly been reported as examples of occlusion of the posterior inferior cerebellar artery and in such there is no difficulty in comprehending the reason for contralateral sensory loss on the trunk and face. If these propositions are accepted there is nothing to invalidate the hypothesis that the fibres of the quintothalamic tract pursue their course through the medulla oblongata in company with the fibres of the medial lemniscus.

It only remains to comment on the lack of evidence in Case 2 for the existence of a dorsal quintothalamic tract. In this case the lesion attained its greatest proportion cephalad to the decussation of the pyramids and therefore, according to Wallenberg and van Gehuchten, it affected that part of the nucleus of the spinal tract of the trigeminal nerve which, in the rabbit, gives origin to the dorsal quintothalamic tract. It is fair to question whether or not their experimental lesions were sufficiently circumscribed. From the illustrations which they give it is evident that the experimental lesions damaged much more than the nucleus of the spinal tract. In particular they seem to have paid little attention to the descending vestibular root and it is possible that the fibres described by them as the dorsal quintothalamic tract were, in reality, fibres connecting the descending vestibular root with the medial longitudinal bundle. The danger of such confusion was remarked on by Winkler and he hinted that this confusion had probably taken place.

In short the inferences drawn from a critical survey of previous experimental and pathological observations are in congruity with those deduced from the facts demonstrated in Case 2 of this report. Both indicate that in man the bulbar portion of the central trigeminal pathway is a crossed tract which, in the medulla oblongata at least, is incorporated with the fibres of the medial lemniscus. Cephalad to the mid-level of the pons it is probable that the fibres of the quintothalamic tract taking origin in the spinal nucleus come into a closer anatomical relationship with the fibres of the spinothalamic tract.

The central reflex pathway of the trigeminal nerve.—According to Cajal this tract, consisting of short neurones, both crossed and uncrossed. links up the trigeminal nerve with the motor nuclei of the brain stem. Winkler described a double connection between the spinal nucleus of the trigeminal nerve and the ipsilateral nucleus of the facial nerve, first a long caudal afferent arc through the most caudal part of the spinal tract and, secondly, a short direct afferent arc at the most cephalad level of the medulla oblongata, but evidence that similar conditions apply in man has never been obtained. A survey of the published cases of the retro-olivary syndrome shows clearly that the corneal reflex once lost is lost for ever. In the majority of these cases there are good grounds for assuming that the syndrome was due to occlusion of the posterior inferior cerebellar artery and that the more cephalad levels of the medulla oblongata were unaffected by the lesion. From this it appears that in man the afferent arc of the corneal reflex is in the fibres of the ophthalmic nerve which pass to the most caudal part of the spinal tract. The evidence of the cases here reported enforces the correctness of this opinion. It is true that in Case 1 an extremely feeble corneal reflex was probably present. However, in syringobulbia it is difficult to be certain that every fibre has been destroyed in the immediate vicinity of the disease process and in this case it is possible that a few fibres of the ophthalmic nerve did, in fact, attain the most caudal part of the spinal tract. In Case 2 the most cephalad levels of the medulla oblongata were intact and, had a proximal reflex arc existed, there would have been no obvious explanation for the loss of the corneal reflex. Finally the complete abolition of the corneal reflex after section of the spinal tract in Case 3 and the similar findings in Sjöqvist's personal series of cases admits of only one explanation. Ever since the researches of G. and F. Hoggan (1883) on the nature of the nerve endings in the cornea it has been believed that the cornea is supplied solely with pain fibres. Their observations, taken in conjunction with the behaviour of the corneal reflex in lesions of the spinal tract of the trigeminal nerve, give further proof that the fibres of the ophthalmic nerve pass to the most caudal part of the spinal tract of the trigeminal nerve.

The Qualities of Sensation Mediated by the Spinal Tract of the Trigeminal Nerve.

(*a*) *Pain and thermal sensibility.*—Since the publication of the case of occlusion of the posterior inferior cerebellar artery by Hun (1897) it has been universally accepted that pain impulses from the face are mediated exclusively by the spinal tract of the trigeminal nerve. It has been equally accepted that thermal impulses pursue a similar course although it has often been suggested that the paths for heat and for cold are to some extent independent both of each other and of pain. A degree of differential thermanæsthesia was present in Case 1 where, it be remembered, loss for cold was greater than for heat. This partial and differential thermanæsthesia coincided with a moderate degree of hypoalgesia. In the territory of the ophthalmic nerve there was almost total thermanæsthesia and analgesia. In this connection Case 3 was even more interesting for, in the territory of the right maxillary nerve, there was total analgesia and only a very moderate degree of thermanæsthesia. Few though these observations are it seems justifiable to conclude that thermal sensibility is represented in the spinal tract exactly as is pain, that is in terms of the peripheral divisions and in an inverse order. Further, the slight thermanæsthesia and total analgesia in the maxillary territory in Case 3 would be explicable on the assumption that thermal sensibility is mediated by a portion of the nucleus of the spinal tract situated rather cephalad to that concerned with the mediation of pain impulses.

(*b*) *Pressure pain.*—In regard to the possible pathways mediating pressure pain the most diverse views have been, and are, held. The apparent preservation of pressure pain following excision of the trigeminal ganglion or section of the sensory root has led many to believe that impulses underlying pressure pain travel centrally independently of the trigeminal nerve. Thus, it has been suggested by Davis (1923) that pressure pain from the face travels in the facial nerve. Others have sought a solution in the suggestion that the sympathetic nervous system may be the conductor. As a matter of fact neither clinical nor experimental evidence lends the least support to either of these views. A recent paper by Carmichael and Woollard (1933) goes far to clarify the position. They too, were puzzled by the apparent preservation of pressure pain following successful alcohol injection of the trigeminal ganglion until they discovered that the presence or absence of proper support for the subject's head and neck profoundly influenced the results. They found that if the head and neck were rigidly supported pressure pain was lost and they attributed previous contrary findings to the tension set up in the neck muscles by reason of absent or inefficient support to the head and neck. It is very regrettable that pressure pain was not estimated in Case 1 but in Case 3 it was carefully tested. It was found that after operation there was complete absence of pressure pain in the analgesia area. This was beautifully demonstrated on the right cheek by placing two fingers within the patient's mouth, thereby producing a proper counterthrust to the algometer. In this case, therefore, it seemed clear that impulses underlying pressure pain followed a course indentical with that for superficial pain.

(*c*) *Touch.*—There has been much uncertainty regarding the possible pathways for touch. No one has denied that destruction of the spinal tract of the trigeminal nerve often leaves touch perfectly intact but this in no way proves that the main sensory nucleus is the sole receptor for tactile impulses. On the analogy of the condition in the spinal cord it has often been suggested that, in the trigeminal nerve, there exists a dual pathway for touch. From a consideration of a case of presumed disseminated sclerosis of very unusual type Spiller (1915) concluded that tactile impulses pass exclusively to the main sensory nucleus but, unfortunately, post-mortem verification was lacking.

Another problem requiring explanation concerns the frequency with which some degree of tactile anæsthesia is reported in cases where the lesion is proved to have been confined to the spinal tract. There is no need to cite specific instances. They comprise many cases of syringobulbia, for example the two reported by Taylor, Greenfield and Martin and already referred to, and many instances of occlusion of the posterior inferior cerebellar artery. A consideration of the following facts suggests that such observations may probably be fallacious. Now tactile anæsthesia is unknown in the case of lesions confined to the medulla oblongata, when loss for touch has been reported in such cases it has always been partial. The method employed in testing tactile sensibility is always of vital importance and nowhere more so than on the face. As ordinarily carried out with a wisp of cotton wool touch and tickle must almost inevitably be confused. Personal experience in patients with facial hemianalgesia has shown that they will always describe the contact of cotton wool as "less plain" or "not so strong" on the affected side. If now the sense of touch be tested with von Frey's hairs it is found that the lightest contacts are readily perceived. These facts compel a measure of scepticism in regard to the assertion that lesions of the spinal tract of the trigeminal nerve may be responsible for impaired tactile sensibility. Only careful testing with a method designed to exclude the factor of tickle will settle this question. In Cases 1 and 3 tactile sensibility was carefully estimated and it was found that on the analgesic areas the lightest contacts were felt as readily as in areas of intact sensibility. These observations do not, of course, prove that tactile impulses pass exclusively to the main sensory nucleus. On the other hand if any do travel in the spinal tract their importance must be small, so small indeed that their entire exclusion causes no appreciable rise in the threshold for touch.

(*d*) *Tactile discrimination.*—Only in Case 3 was the state of tactile discrimination investigated. Before operation the patient readily perceived two points at a separation of 0·5 to 1·0 cm. simultaneously applied in the region of the lips and cheeks and on the forehead. On re-testing the analgesic areas after operation the state of tactile discrimination was found entirely unaffected. This observation suggests that discriminative aspects of sensibility have no important representation in the spinal tract of the trigeminal nerve. It is in keeping with the opinion that these higher discriminative functions are represented in the main sensory nucleus, an opinion which is completely in harmony with the phylogenetic history of this nucleus.

SUMMARY.

A critical and historical review has been made of the clinical, pathological and experimental evidence bearing on the nature of the segmental representation of the spinal tract of the trigeminal nerve and on the position of the quintothalamic tract. Evidence bearing on the probable qualities of sensation mediated by the spinal tract has also been considered. On none of these problems is there general agreement; indeed opinion is more divided to-day than at any previous time. The clinical and pathological findings in three cases (syringobulbia, occlusion of the posterior inferior cerebellar artery, operative section of the spinal tract of the trigeminal nerve) are fully reported, particularly in so far as they shed light on these problems. The observations recorded are discussed in the light of previous observations.

CONCLUSIONS.

(1) In the human subject circumscribed vascular lesions are of paramount value in affording precise information on the anatomy and physiology of the brain stem. Because of the haphazard incidence of the lesion at different anatomical levels the evidence drawn from cases of syringobulbia must be closely scrutinized but, if rigid precautions are observed, valuable information may be obtained.

(2) The opinion that the representation in the spinal tract of the trigeminal nerve is in terms of concentric zones converging on the nose and mouth has been based exclusively on observations in cases of syringobulbia and, generally, in the absence of thorough post-mortem verification. No example of the retro-olivary syndrome, of vascular origin, has ever supported this opinion. In circumscribed vascular lesions of the retro-olivary region the distribution of sensory loss in the ipsilateral trigeminal territory is invariably in terms of the peripheral divisions of the trigeminal nerve.

If a lesion implicates the most caudal part of the spinal tract of the trigeminal nerve the resulting analgesia is limited to the territory of the ophthalmic nerve. If the lesion extends further cephalad (perhaps to the level of the most caudal rootlet of the glossopharyngeal nerve) analgesia is limited to the territories of the ophthalmic and maxillary nerves. Finally, if the lesion implicates the spinal tract still more cephalad the resulting analgesia invades the whole of the trigeminal territory. These observations are incompatible with the opinion that the representation in the spinal tract is in terms of concentric zones converging on the nose and mouth. On the other hand they afford strong evidence in support of the hypothesis that the segmental representation in the spinal tract is in terms of the peripheral divisions and that the order of central representation is the inverse of the peripheral.

(3) These observations afford no evidence in favour of the existence of a dorsal quintothalamic tract; neither do they lend support to the hypothesis that the quintothalamic and spinothalamic tracts pass through the oblongata in close anatomical relationship. The observations made in one case (Case 2) justify the opinion that in the human subject the quintothalamic tract is entirely crossed and that it ascends through the medulla oblongata incorporated with the medial lemniscus. There is some evidence that the quintothalamic fibres occupy the ventromedial part of the medial lemniscus in the medulla oblongata and that finally, in the cephalad half of the pons, they come into fairly close anatomical relationship with the fibres of the spinothalamic tract. If this hypothesis be correct normal sensibility in the contralateral trigeminal territory in occlusion of the posterior inferior cerebellar artery is easily comprehended. It is suggested that the occurrence of contralateral sensory disturbance in the trigeminal area in vascular lesions results, not from occlusion of the posterior inferior cerebellar artery, but from occlusion of some other vessel.

(4) The abolition of the corneal reflex in these cases suggests that the afferent arc descends to the most caudal part of the spinal tract. If a shorter and more cephalad afferent arc exists in man it appears to be insufficient of itself to maintain the integrity of the reflex.

(5) Pain and thermal sensibility are mediated exclusively by the spinal tract of the trigeminal nerve. There is some evidence that the part of the nucleus of the spinal tract concerned with the mediation of thermal stimuli lies somewhat cephalad to the part concerned with the mediation of pain.

(6) Superficial and deep pain pursue an identical pathway in the spinal tract. There is no necessity to suppose that the facial nerve or the cervical sympathetic nerves play any part in the conduction of impulses underlying pain sensibility.

(7) The recognition of touch and the discrimination of two points simultaneously applied are independent of the spinal tract. Impulses

underlying these discriminative aspects of sensibility are, in all probability, mediated exclusively by the main sensory nucleus.

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A CHEMICAL STUDY ON FLUIDS OBTAINED FROM CEREBRAL CYSTS: REPORT ON FIFTY-SIX CASES.[1]

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CEREBRAL cysts occur with considerable frequency; according to statistics by Martin (1923) from Cushing's clinic, cystic gliomas represent 30 per cent. of all gliomas and 13 per cent. of all cerebral tumours. In spite of this, little work has been done on the fluid contents of cysts from a chemical point of view. Folin, whose results are reported in the same paper, examined the cyst fluids of seven cases of gliomatous cysts. His estimation of various fractions of non-protein nitrogen gave the following average results:—

N of amino acids	5·3 mg. per 100 c.c
N of urea	12·4 mg. per 100 c.c.
N undetermined	6·7 mg per 100 c.c.
Total N (non-protein)	24·7 mg. per 100 c.c

If the cyst fluid were produced by breakdown of tissue only, one would expect much higher readings of amino acids. Therefore Martin explained the results as due to transudation from the blood. The following investigation was undertaken: (1) To obtain average results of various constituents of cerebral cysts; (2) to estimate their diagnostic value; and (3) to contribute to the theory of cyst formation.

METHODS AND MATERIAL.

In fifty-six cases the cyst fluid was examined chemically. The fluid was usually obtained at operation, but in a few cases it was obtained at post mortem. The specimens were cleared by centrifuging. Whenever it was possible, duplicate estimations were undertaken. In a number of cases parallel estimations of the blood were carried out. The blood was obtained from veins of the arm or leg, usually a few hours after the operation, or in a few cases during the operation—that is to say, almost simultaneously with the withdrawal of cyst fluid. The number of chemical constituents examined depended on the amount of available material.

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[1] This investigation was carried out while holding the Kathleen Schlesinger Fellowship.

Substance	Number of estimations	Parallel estimations in the blood	Parallel estimations in the ventricular fluid
Albumin and Globulin	21	11	—
Cl.	45	15	3
Ca.	25	5	3
Mg.	26	7	4
Glucose	7	—	1
Urea	12	8	1

For albumin and globulin the method of Greenberg (1929) was applied. Calcium was estimated according to Kramer and Tisdall (Harrison, 1937), magnesium and chlorides according to McCance and Shipp (1933), glucose according to Folin and Wu, and urea according to Archer's modification of Folin and Wu's method (Harrison, 1937).

RESULTS.

The results are given in detail in the accompanying tables. It can be seen that the protein content of the cyst is always lower than that of the blood. The globulin in the cyst fluid is usually low, so that the albumin/globulin ratio amounts to an average value of 3·7, compared with the average ratio in the blood protein readings of 2·8. This is particularly remarkable in two tumours of mesodermal origin (Co. 21.4.36 and Hu. 7.5.37), in which the albumin reading in the blood and cyst is identical, and the globulin content of the cyst is lower. During puncture or incision of the cyst a mixture of the cyst fluid with cerebrospinal fluid cannot be avoided in every case; this accounts for the comparatively low protein reading in case "Mi. 8.6.38," and it may account for a few other exceptionally low protein readings. The amount of chloride is constantly higher in the cyst fluid than in the blood, with the exception of one case in which the histological diagnosis was that of a cystic condition of the choroid plexus of unknown nature. The calcium content is either that of the blood calcium or lower, between 6·6 and 10·4 mg. per cent. In the case of a cystic oligodendroglioma, however, it amounted to 11·4 mg. per cent. Magnesium, with the exception of one low reading (1·23 mg. per cent.), ranges between 2·18 and 4·1 mg. per cent., that is to say, it corresponds with the normal magnesium content of the blood. The differences between blood and cyst fluid in the individual cases, however, are irregular. Urea shows a similar behaviour to calcium. It corresponds with the blood urea or is somewhat lower (two cases). For technical reasons, simultaneous parallel estimations of glucose in the blood could not be made; the amounts of glucose in the cysts, however, are either readings corresponding to the blood sugar of average individuals, or somewhat below it.

TABLE I.

Name and date	Material	Alb. g. %	Glob. g. %	Chlorides as NaCl. mg. %	Ca. mg. %	Mg. mg. %	Diagnosis and Notes
Sm. 3.6.38	Cyst Blood	1·33 4·1	0·40 2·99				Parieto-temporal cyst, histology unknown
J. G. 7.6.38	Cyst Blood	3·98 5·84	1·61 3·98	571 543			Cancer of lung, secondary in R. hem., cystic
Wo. 16.6.38	Cyst Blood	1·46 4·51	0·69 1·72				Cerebellar cyst
Wo. 21.6.38	Cyst Blood	2·66 5·48	0·75 1·6	643 590			Cerebellar cyst
Yo. 16.7.38	Cyst	3·98	1·73	578			Parieto-temporal cyst (? glioma)
Yo. 21.7.38	Cyst Blood	3·98 5·57	1·38 1·5	580 557			
M. C. 21.4.36	Cyst Blood	4·78 4·78	0·92 1·84				Cystic neurofibroma, R. ponto-cerebellar angle
C. J. 22.9.36	Cyst Blood	6·9 7·24	0·92 2·30	796	10·0 10·4	5·91 4·18	Cystic glioma, parietal
Ha. 14.10.38	Cyst Blood	3·79 4·30	1·29 1·61				Subdural hæmatoma
Ad. 21.4.36	Cyst Blood	1·33 4·20	0·23 1·1				Polar spongioblastoma
Pe. 14.7.36	Cyst Blood	3·45 4·94	1·15 1·44				Suprasellar cranio-buccal cyst, simple epitheloid
Hu. 7.5.37	Cyst Blood	3·19 3·19	0·82 1·61	585 410	9·4 9·8	2·58 2·53	Recurrent cerebellar cyst. Hæmangioblastoma
Mi. 8.6.38	Cyst	1·06	0·40	655			Glioma of basal ganglia. Cyst fluid obtained p.m., mixed with c.s.f.
E. J. 30.6.38	Cyst	3·98	0·80	524			Parietal cyst (histology unknown)
Co. 5.7.38	Cyst	2·92	1·72	623			Chromophobe adenoma of pituitary. Cyst fluid obtained p.m.
Fr. 15.7.38	Cyst	4·25	0·75	730			Cystadenoma of infundibulum Cyst fluid obtained p.m.
Me. 21.7.38		2·17	0·35	676			Left parietal cyst
Pu. 28.9.38	Cyst	4·25	1·1				Parietal astrocytoma
Pe. 7.10.38	Cyst	4·14	1·05				Cyst fluid obtained p.m., very blood-stained, hæmolysis
Ma. 10.10.38	Cyst	3·50	1·34				Epithelial tumour of Rathke's pouch. Cyst fl. obtained p.m.
Ch. 6.10.36	Cyst	6·39	1·3				Cerebellar astrocytoma

TABLE II.

Name and date	Material	Ca. mg. %	Mg. mg. %	NaCl mg. %	Glucose mg. %	Urea mg. %	Diagnosis and Notes
Ad. 21.4.36	Cyst Blood	6·6 10·4	1·23 3·08	646			Fronto-parietal spongioblastoma
L. J. 23.3.37	Cyst Blood Ventr fluid			540 477 702			R. temporal astrocytoma
Al. 25.7.37	Cyst Blood			562 406		32 43	R. frontal gliomatous cyst
A. T. 11.2.38	Cyst Ventr. fluid			646 746	53 70	24 27	Cerebellar astrocytoma
C J. 22 9.36	Cyst Blood	10·0 10·4		796			Parietal glioma
Ag. 5.6 36	Cyst Blood R. vent. fluid		3·07 2·52 3·07				Suprasellar fibrous astrocytoma
Ho. 1.10 36	Cyst Ventr. fluid	7·6 4·0	4·1 3·44	671·6			R. temporo-parietal glioblastoma
Fr. 29.8.36	Cyst Ventr. fluid	9·2 6·4	2·18 2·18				Ventricular tumour in tuberous sclerosis
Ma. 12 3.37	Cyst Blood	9·8 9·5					Parietal astrocytoma
Ba. 6.1.38	Cyst Blood			613 522	55	18 22	Simple cyst of Rathke's pouch
Co. 18.1 38	Cyst Blood			599 629	103	54 54	Cystic condition of choroid plexus
J. R. 25.11 37	Cyst Blood	10·4	2·48 2·46	617·6 603·7			R. ponto-cerebellar angle hæmangioblastoma
R. F. 2.3.37	Cyst Blood	8·0 9·0	2·78 2·21	552 559			R. parietal cyst, hæmangioblastoma (?)
St. 10.7.36	Cyst Blood		3·05 2·56				Secondary (intestinal ?) tumour of cerebellum
Wa. 4.2.38	Cyst Blood					70 72	Secondary from bronchial carcinoma
Hu.(1st op.) 7.5.37	Cyst Blood	9·4 9·8	2·58 2·32	585 410			Recurrent L. cerebellar cyst; hæmangioblastoma
2nd op. 8.6.37	Cyst Blood		2·48 4·46	612 557			
3rd op. 5.11.37	Cyst	9·4	2·2[illegible]	643			

TABLE II.—*Continued.*

Name and date	Material	Ca. mg. %	Mg. mg. %	NaCl. mg. %	Glucose mg. %	Urea mg. %	Diagnosis and Notes
Hi. 17 12.37	Cyst Blood			662 634	67	20 19	Cerebellar cyst. Nature unknown
Le. 23.12.36	Cyst Blood	10·4	2·65	590 515			Frontal cyst. Brownish fluid full of cholesterin crystals, Hist.: Fibrous tissue with some calcareous masses
Wi (1st op.) 30.11.37	Cyst Ventr. fluid	8·0 3·4	2·97 3·58	569 744			Occipital cyst. Nature unknown
2nd op. 21.1.38	Cyst Blood			590 585		31 29	
Ap. 24.1.38	Cyst Blood			569 569		25 35	Occipital cyst of unknown origin
Hu 4.2.38	Cyst Blood			542 514		29 26	Tumour of cauda equina
No. 25.11.36	Cyst	10·2	3·08	613			Cerebellar astrocytoma. Fluid obtained at p.m.
Cu. 5.3.37	Cyst	11·4	2·13	519			Parietal oligodendroglioma
Ha. 12.3.37	Cyst	7·2	3·05	625			Glioblastoma. R. frontal. Fluid obtained at p.m.
Pe 2 4.37	Cyst	9·2	2·32	526			Diffuse glioblastoma. L. frontal
Ha. 8.6.37	Cyst	8·8	2·95	652			Parietal glioblastoma
Cl 12.7.37	Cyst	7·2	2·09	601			Fronto-parietal glioblastoma
Ho 17.9.37	Cyst	7·6	3·53	632			Cerebellar astrocytoma
Ca 24.9.37	Cyst	9·0	3·32	648			Cerebellar astrocytoma
To. 16 11.37	Cyst	7·8		630			Thalamic astrocytoma
Pa 7.1 38	Cyst			642			Frontal astrocytoma
Cr. 19.4.38	Cyst				77	45	Parieto-frontal astrocytoma
Lo. 24 3.38	Cyst				75	38	Suprasellar cyst, fluid containing cholesterol crystals
We. 24.6.37	Cyst		3·7	492			Acidophil adenoma of pituitary

TABLE II.—*Continued.*

Name and date	Material	Ca. mg. %	Mg. mg. %	NaCl. mg. %	Glucose mg. %	Urea mg %	Diagnosis and Notes
Dr. 11 11.37	Cyst	9·2	2· 2	589			Adamantinoma
Ch. 23.9.37	Cyst	8·6	2·21	585			Cerebellar capillary hæmangioblastoma
Da 22.6.37	Cyst	8·8	2·46	578			Acoustic nerve tumour
Va. 1.7 37	Cyst	10·2	3·32	552			Secondary carcinoma from lung. Temporal.; Fluid obtained at p.m.
Da. 24.12.36	Cyst	9·2	2·95	768			Cerebellar cyst of unknown origin. Hist. . Normal cerebellar cortex
Li. 24.3 38	Cyst			-	62	24	Cerebral cyst, nature unknown. Hist. : Normal septum pellucidum

DISCUSSION.

From the comparison of the readings of the various substances examined with the histological diagnosis, it is apparent that there is no connection between the histological nature of the cyst and the chemical composition of the fluid. The only finding which is conspicuous from this point of view is the fact that the only calcium reading which was comparatively high was that encountered in a case of oligodendroglioma. This is interesting, because of the frequency with which calcium deposits are found histologically in these tumours. Only investigations on the basis of a larger amount of material of the same sort can prove whether this single finding was a mere coincidence, or whether it has any diagnostic value. A second important point is the complete independence of the chemical composition of the cyst fluid on the site of the cyst, especially on its relation to the cerebrospinal fluid spaces.

The chlorides, with only one exception, were constantly higher in the cysts than in the blood, whereas the protein was constantly lower. How is this regularity to be explained? It has been shown by previous investigators that in transudates from the blood (Loeb *et al.,* 1922, Gollwitzer-Meyer, 1925) this reciprocal proportion is the rule, and that it can be explained on the basis of the Donnan equilibrium. This suggests that the formation of cyst fluids is due to the same mechanism. Moreover, the investigations of Loeb *et al.* showed that in transudates, as well as exudates, calcium, urea and glucose were approximately the same in both blood and fluid. Gollwitzer-Meyer found in transudates (renal and cardial) that the calcium content was always somewhat lower than in the blood. In the present cases of cerebral cysts the amounts of calcium, as well as urea, were either equal to those in the blood or were somewhat lower. In the latter case the calcium ratios between blood and fluid corresponded to those found by Gollwitzer-Meyer in renal and cardial transudates. All this strongly supports the assumption already made that the cyst fluid is derived essentially from the blood. The protein readings, however, are much higher than those of pure transudates as encountered in renal and cardial diseases. They are much more like those of true inflammatory exudates. Schade *et al.* (1926) found total protein quantities of 3·4 to 5 8 grm. per cent. in inflammatory pleural and peritoneal exudates. This corresponds approximately to the magnitude of total protein in cyst fluids. It can be assumed that the histologically abnormal vessels in tumours and the proliferative vascular reaction in the surrounding zone of tumours and cysts provides a state of increased permeability which accounts for those high protein readings. From all this one can draw the conclusion that following the initial colliquative necrosis of tumour tissue the essential process is that of transudation from the blood into the liquefied area ; this, of course, does not exclude the presence of products of break-down in the fluid, but of these very little evidence was found. It is interesting in this connection that the chloride ratio of blood and fluid was the typical one, even in a case of hæmangioblastoma in two examinations at four-week intervals. This supports the view that cysts in hæmangioblastomas are true cysts and do not represent a direct continuation of the intravascular space.

Munro and Merritt (1936) have shown in a study on 105 cases of subdural hæmatoma that the chemical picture of the fluid depends on the age of the cyst. During an initial period the protein increases owing to hæmolysis ; later it decreases owing to a breakdown of protein molecules. An increase of the amount of fluid occurs coincidentally because of the dialysis of fluid from the cerebrospinal fluid space. In the present paper the problem of the formation of subdural hæmatomas was not specially studied as hæmolysis and the adjoining cerebrospinal fluid space appeared to provide somewhat different conditions. It should, however, be stressed that from the survey of the present cases it appears that there is no certain relation between the age of the cyst and the protein content.

SUMMARY.

Estimations of various constituents of cyst fluids in fifty-six cases of cerebral cysts gave the following results:—

The protein content in the cyst fluid is constantly lower than that in the blood, the chloride content being always higher. The calcium content of the cyst fluid either corresponds to that of the blood or is somewhat lower; the same holds true with the urea content. The amounts of glucose correspond to average blood-sugar values, or are somewhat lower.

These findings are analogous to those obtained by previous authors in transudates from the blood other than cyst fluids. The comparatively high amounts of protein which resemble those of inflammatory exudates is explained by the high permeability of pathological vessels and by mesodermal reactive processes. There is no relation between the chemical nature of the fluid on the one hand and the site or histological nature of the cyst on the other. A comparatively high amount of calcium (11·4 mg. per cent.) was found in a cystic oligodendroglioma.

I wish to express my gratitude to Dr. J. G. Greenfield and to Dr. J. N. Cumings for help and suggestions, to Mr. R. F. Nunn, B.Sc., for technical advice, and to the members of the surgical staff for their helpful co-operation.

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SPASTIC DYSPHONIA ("INSPIRATORY SPEECH").

BY MACDONALD CRITCHLEY.

THE purpose of this paper is to call attention to a peculiar disorder of articulation which has been treated somewhat perfunctorily in the literature. This form of speech disturbance has been encountered in a few patients, three of whom are described below. One or two publications give accounts of a dysarthria which suggest the same type of speech-disorder as concerns us here. Numerous descriptive epithets have been applied such as "seelöwen Sprache," but the commonest term has been "inspiratory speech." Various diagnoses have been proffered in these cases, especially disseminated sclerosis, double athetosis, and progressive cerebellar degeneration.

The characteristics of the speech defect may be described as follows: the voice sounds are emitted in a peculiarly harsh and constrained fashion, the pitch being at times unduly low and at others excessively high. The word-sequence is interrupted so that a staccato effect is produced. The volume of the sound seems uncontrolled and words may be spoken too loudly interrupting in an explosive fashion a sequence of subdued tones. At times there is a tremolo effect audible, suggesting a tremulous condition in the respiratory or articulatory musculature. Not only is the pronunciation of the consonantal sounds affected to a slight degree, but the vowel sounds too are modified, differing in this respect from the commoner types of dysarthria. There is an impairment of the so-called "chanson de parler" so that the speech tends towards a monotone. There is always an excessive play of facial expressive movements with the accompaniment of an associated tic-like contraction of the muscles of the neck and jaws, and even of the shoulder-girdle and upper arm. Throughout the act of speaking there appears to be a striking hypertonus in the extrinsic muscles of the larynx which waxes and wanes with the involuntary movements: in this way there results a peculiarly forced character in the speech, which appears difficult of accomplishment, almost as though the patient were trying to talk whilst being choked. Although the whole of the speech takes place during expiration, the sound-effect is unnatural and suggests the picturesque though incorrect title of "inspiratory speech."

The larynx was examined in two of the patients. In one case (No. 1) no obvious abnormality was seen in the palatal or laryngeal muscles, except that the ventricular bands did not come into apposition; there was no evidence of involuntary motor activity. The other patient (No. 3) displayed jerky movements of the vocal cords, analogous with a series of clonic movements of the palate and tongue associated with the act of phonation.

It is possible that this type of speech was present in the first case recorded by Ramsay Hunt (1914) of " dyssynergia cerebellaris progressiva." The author described the speech as slow, scanning and frequently interrupted by violent explosive efforts and utterances. Under excitement these rendered the speech almost unintelligible. The act of speaking was associated in this case with tremulous contraction of the face and increased tremor of the head. In the other two cases described by Ramsay Hunt, the speech affection did not resemble the type under discussion.

Most relevant, however, are the descriptions of dysarthria made by Schuster (1924) in his cases of senile cerebellar degeneration. His first patient, a woman of 71, showed an explosive, nasal, slowed, scanning speech. Labials were especially badly pronounced. In the middle of a phrase or a word, the loudness of the voice might suddenly increase or decrease. The speech was mainly monotonous and there were frequent false intonations. It was difficult to understand what she said. There was a tremor of the head which increased as she spoke. In his second case, a woman of 63, the speech was described as slow and scanning, with interruptions in the middle of a word. Clonic movements of the head often synchronized with a jerkiness of the speech. The third patient, a woman of 58, spoke slowly with a loud explosive, nasal dysarthria, as though someone were clutching her by the throat while she was trying to speak. Schuster also referred to a similar dysarthria occurring in two patients with cerebellar vascular lesions, and in a third patient who showed a delayed form of heredo-familial cerebellar ataxia. The author emphasized that the dysarthria differed from the usual scanning speech of cerebellar disease . . . " Die Sprache unserer Kleinhirnkranken errinerte zwar die gewöhnlich als 'skandierende' Sprache bezeichnete; denn sie war gleichfalls sehr verlangsamt, gedehnt und schwerfälling; sie hatte aber ausserdem noch eine besondere Note, welche keiner der bekannten anderen Sprachstörungen zukommt, und welche sich schwer beschreiben lässt. Sie klang ungefähr so, als wenn jemand, denn man die Gurgel zuhält, mit aller Kraft und Anstrengung zu sprechen versucht, sie war überlaut und in ihrer Klangfarbe gänzlich won den normalen verschieden. Häufig kamen dabei inspiratorische, leicht schluchzende Töne vor, die man normalerweise überhaupt nicht aus dem menschlichen Kehlkopf vernimmt, sondern wie man sie etwa bei dem eigentümlichen Bellen der Seelöwen hört. (Diesen eigentümlichen 'Seelöwenton' habe ich nur noch einige Male bei Patienten mit Athetose double vernommen.)"

It may be that this same variety of speech was familiar to Meige. This author, who has devoted much attention to disorders of speech, has analysed closely the processes at fault (1928). He distinguishes faulty habits of pronunciation from various disorders of elocution. Of the latter, he recognizes (1) an atonic or inhibitory type; (2) a tetaniform or tonic convulsive variety (= stammering); and (3) a palisyllabic or clonic convulsive type (=stuttering). Concomitant motor symptoms, such as tic-like grimacing may occur in each. With regard to the vocal manifestations of the elocutionary disorders, defects can be traced in the mechanisms of respiration (dyspneumia), phonation (dysphonia) and articulation (dysarthria). Meige points out that the ætiology is complex and that all these may be encountered in a number of organic affections of the nervous system. A case record of his own (1914) entitled "Dysphasie singultueuse avec réactions motrices tetaniformes et gestes stéréotypes" deals with a speech affection in a girl of 13 which seems to resemble that occurring in the third of the patients here described.

PERSONAL CASES.

No. 1.—L. L. J., male, aged 28, was admitted to King's College Hospital from September 1 to November 29, 1937

In 1932 whilst in the Royal Navy, he accidentally sucked up some petrol from a pipe, so that the naval surgeon had to wash out his stomach Thereafter he noticed a tremor in the left hand. Examination at that time revealed exaggerated knee and ankle jerks and intention tremor of the left upper limb. There was some doubtful pallor of the outer halves of the optic discs. The blood and spinal fluid were normal. He was discharged from the Navy the same year as a suspected case of disseminated sclerosis.

Eighteen months later he enlisted in the Army. One day, however, he found while on parade that he was unable to keep his head turned to the front . . . "When we had to present arms everyone faced the front but me." As a result he was re-examined and invalided out of the Army in July, 1934. By this time, the tremor had increased in the left arm and two months later the involuntary turning movements of the head became worse. At this time he first began to have trouble with his speech.

Family history.—His father had died of phthisis; the mother was said to "fall about." There were two brothers and one sister, as well as three step-brothers and one step-sister, all of whom were described as normal.

Examination.—The patient showed a spasmodic torticollis, with jerkings of the chin upwards and to the left, and with myoclonic movements of small range in the muscles around the right corner of the mouth. The outstretched hand displayed on the left side a rhythmic tremor, considerably increased on voluntary movement. None of the arm-jerks was obtainable except the left triceps reflex. There was no defect of tonus or of motor power in the legs. The knee-jerks were present but the ankle-jerks absent; plantar responses were flexor. Abdominal reflexes intact. The temporal portions of the optic discs were possibly a little too pale. All forms of sensation were somewhat impaired over the left half of the body.

The *speech* was hoarse and jerky, the sounds being breathless and constrained. The vowels were pronounced imperfectly. Towards the end of a sentence the voice tended to become less audible.

X-ray screening of the chest revealed that the movements of the diaphragm during respiration and speech were normal with no evidence of tremor.

Examination of the pharynx and larynx (Mr. Victor Negus): "No abnormal movements of the palate, which moves well and apparently quickly. Palato-glossus and palato-pharyngeus contract well on both sides. Posterior pharyngeal wall rises well on phonation. Larynx moves upwards on 'ee' and remains in mid-line. Vocal cords move well and equally on phonation. Larynx opens widely on normal respiration. No nystagmus of larynx. I do not think he speaks during inspiration . . . I think the disorder of speech is due to inco-ordination of respiration and articulation."

Cerebrospinal fluid.—Initial pressure 120, rising to 300 on jugular compression Less than two cells per cubic millimetre; protein 40; chlorides 720. Wassermann negative.

The patient was regarded as having a striato-cerebellar affection with symptomatic torticollis. Disseminated sclerosis was regarded as improbable.

No. 2.—J. S., male, aged 42, first attended the out-patient department of the National Hospital, Queen Square, in November, 1921. He was admitted under the care of Dr. Kinnier Wilson between April 13 and July 14, 1933, with the diagnosis of disseminated sclerosis.

Weakness of the legs had developed gradually since 1918, and since 1923 there had been unsteadiness in walking. The arms became weak and clumsy in 1928, and since 1927 there had been at times urinary and less often rectal incontinence. Difficulty in speaking first became apparent in 1921.

The family history was negative in respect of nervous disease.

Examination.—There were a few irregular nystagmoid movements on full lateral deviation of the eyes. Both legs were spastic and somewhat weak. The lower abdominal reflexes were sluggish; knee and ankle jerks exaggerated; both plantar responses extensor. Except for some diminution of postural sensibility in the lower limbs, sensation was normal.

Cerebrospinal fluid.—One cell per cubic millimetre; protein 75; Nonne-Apelt negative; Pandy weakly positive; Lange, no change; Wassermann negative in fluid and in blood.

The speech was described in 1921 as "strained, high-pitched, slightly staccato—as though speaking in inspiration."

According to the notes made in 1933, the speech was "guttural, low-pitched, spastic and unvarying . . . no evident dyspnœa at rest or in talking."

No. 3.—E. G., male, aged 40, was a patient at the National Hospital, Queen Square, under the care of Dr. W. Aldren Turner from May 5 to July 16, 1925. Three years before he had been an in-patient of King's College Hospital (Dr. Tunnicliffe) for the same disorder.

At the age of 15, some fireworks had been surreptitiously attached to his coat-tails and then lighted. The resulting fright was intense and trouble with articulation dated from that incident. Previously he had won prizes at school for elocution. Weakness and spasm in the arms and hands first appeared in 1914, that is at the age of 29. Twitching of the face first developed in 1921.

According to his wife, the patient's speech was abnormal when she first knew him, i.e. twenty-two years before, but the hands were not affected until about four years ago.

Family history.—Eleven children , one was said to stutter and to have deformed feet ; another showed excessive sleepiness.

Mother died from a stroke ; the father, aged 69, suffered from a similar though slighter affection of the speech ; there was no trouble with his arms (the wife stated that her father-in-law's speech was gruffer than her husband's and that he did not contort his face as he spoke ; neither did he stammer).

It is believed that the paternal grandmother had a tremor of the hands and an affection of the speech.

One brother and one sister were alive and quite healthy.

Examination.—Very fine lateral tremor of the mandible ; slight relative weakness of the left side of the face. The head was held tilted slightly over to the right, but there were no clonic involuntary movements. Coarse fibrillary tremors were present in the tongue. When the patient phonated, the tongue shot in and out and the palate rose and fell in a series of parakinetic movements.

Both hands were held with the fingers flexed into the palms. Tonus was increased in the distal parts of the upper limbs Under emotional stress and on voluntary movement both hands showed a coarse, irregular, undulating tremor of the fingers, more evident on the right side. Voluntary power was good except for an inability to extend the fingers All digital movements were awkward, inco-ordinate and slow.

Sensory testing revealed no abnormality. All the tendon-jerks were present and equal , abdominal responses elicited ; plantar reflexes flexor.

Cerebrospinal fluid.—Five cells per cubic millimetre. Protein 40. Lange 0001110000. Wassermann negative in fluid and blood.

Larynx (Mr. Theodore Just).—" Abduction and adduction of cords full ; the movements are jerky and are similar to the movements of the tongue and palate."

Speech.—The articulation was grossly defective and inco-ordinate so that it was only with the utmost difficulty that one could understand him. When he attempted to speak he would tilt his head to the right and screw up the left eye. The face would then show a series of extraordinary grimaces and the complexion become flushed. " Speech is pre-eminently inspiratory in type, is grossly inco-ordinate and breathless. Occasionally he stammers over a syllable. Labials and dentals are uttered in an explosive fashion There is a tendency for the syllables to be separated in a staccato fashion. During the effort of speaking the right arm shows a series of involuntary movements."

The diagnosis of double athetosis was hazarded. (In King's College Hospital the condition was regarded as probably an hysterical affection.)

Discussion.

In the three cases here described a clinical diagnosis cannot be arrived at with certitude. The first two patients were regarded, at one time at least, as suffering from disseminated sclerosis. This is probably not the correct explanation of the symptoms in the first case and the diagnosis is not unassailable in the second. The third patient was never diagnosed with any degree of confidence and it is open to argument whether indeed any organic neurological affection existed.

Similar speech disorder has been described by Schuster in cases of senile cerebellar degeneration; cerebellar vascular disease; delayed cerebellar ataxia; and double athetosis. One of Ramsay Hunt's cases of so-called dyssynergia cerebellaris progressiva may be quoted in this connection. Some of the more complex cases of stammering and stuttering recorded by Meige suggest a somewhat similar type of speech.

In most of the cases there were evidences of cerebellar dysfunction. The presence of hypertonus and involuntary movements complicates the picture, however, and suggests that pyramidal lesions may be coexistent in some cases, and extrapyramidal motor disease in others. Although inco-ordinate respiration is demonstrable in the speech of most patients with cerebellar and with striatal affections, the speech disorder which concerns us here differs considerably from what is commonly encountered.

Terminology presents various difficulties, for it is not easy to suggest a word or phrase which clearly expresses the peculiarities of this speech disorder. "Inspiratory speech" had the merit of drawing attention to an unusual type of dysarthria and of attempting to describe its clinical peculiarities; unfortunately its use is unjustifiable as it is essentially inaccurate. Even the term "dysarthria" can be criticized as the articulation of consonants is less severely disordered than the pronunciation of vowels. The trouble concerns phonation as least as much as articulation. Because of the peculiar strained or forced character of the voice, suggesting a spasmodic action of the intrinsic and extrinsic laryngeal musculature, the term "spastic dysphonia" is perhaps least open to objection. The alternative terms "dystonic dysphonia" or "dystonia-dysarthria" are perhaps too cumbersome.

The general question of respiration in normal and disordered speech merits some attention. Under physiological conditions, the act of speaking both in quiet conversation and in declaiming, takes place entirely during the expiratory phase of breathing. The lungs refill by means of a deep inspiration quickly and unconsciously made during pauses in the oration.

In singing this becomes a matter of some difficulty, and may cease to be a purely automatic activity. Training ensures a correct co-ordination between the acts of respiration and of voice production. Indeed, only in whispered speech is it possible to speak upon an inspiratory phase.

In various pathological states, and especially in cerebellar syndromes, there is a considerable disturbance not only in the harmonious working of the numerous articulatory muscles but also in their co-ordination with the respiratory musculature. The resulting dysarthria therefore betrays frequent faults in breathing; the voice is emitted either too loudly or too softly, and the patient soon becomes breathless. At no time, however, does the patient consistently articulate during the phase of inspiration.

Nevertheless, inspiratory sounds may participate in the cries and utterances of various animals, e.g. donkeys and horses, due, as Negus (1929) has pointed out, to the feeble valvular nature of their larynx. The purring of some of the cat tribe takes place during both inspiration and expiration. A bird, of course, can easily produce sounds during both phases of respiration, because of the anatomical nature of the syrinx and its connection with capacious air sacs. In addition various sounds and interjections of an inspiratory character may find their way into human speech as occasional utterances, thus constituting fragmentary exceptions to the rule.

The best instance of the persistent occurrence of inspiratory sounds in articulate speech is encountered in the Hottentot group of languages. The "cerebral," dental, labial, and palatal "clicks" typical of that philological group are mainly inspiratory sounds and in normal speech they interrupt the ordinary stream of expiratory utterance.

In the near East, and especially Turkey, a palatal clicking sound, made on inspiration, is commonly used in association with a backward jerking movement of the head to denote negation. This can be regarded less as a form of speech than an audible gesture.

Hissing inspiratory sounds made by an indrawing of the breath between the closed teeth, may constitute a type of "inferior speech" in the sense of Hughlings Jackson. They are well known in Japan as an audible "honorific" expression denoting respect. The same hissing noise is sometimes used as an interjection signifying assent and is common in this connection in Devonshire. According to Cranz (1873) Greenlanders also have a sound to express pleasurable affirmation, made by sucking air down their throats. Some other primitive languages, as in Tierra del Fuego and in parts of North West America, include strange clucking, grunting and gurgling noises, some of which are inspiratory.

SUMMARY.

Attention is directed to an uncommon and peculiar type of speech-affection, whereby the voice is emitted in a constrained, forced, and barely intelligible fashion. There is also an imperfect modulation of the voice together with a faulty pronunciation of vowel and consonantal sounds. Frequently tic-like contractions of the face, neck, and even upper limbs may accompany the act of speaking.

A few records have been found in the literature describing this type of speech in association with various disorders, e.g. progressive cerebellar degeneration, and double athetosis. Three personal cases are here described wherein this type of speech occurred ; no confident diagnosis could be made in these cases.

The term "spastic dysphonia" is suggested as a clinical descriptive epithet. In the past, the expression "inspiratory speech" has been used, but incorrectly, for the whole of the speech takes place during the phase of expiration, as ordinarily.

Short mention is made of the exceptional instances of inspiratory sounds in human and animal speech.

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THE CLINICAL RECOGNITION OF PICK'S DISEASE: REPORT OF THREE CASES.

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DURING the past few years there has been an increasing number of publications dealing with that variety of heredopathic involution described by Pick. New facts have been brought to light by research along anatomical as well as genetic lines. The recognition of clinical sub-types, and the more thorough clinical descriptions of the disease have rendered diagnosis of the cases easier. Nevertheless, in early cases where symptoms are few, diagnosis may present serious difficulties. In such cases it may be necessary to resort, not only to Neisser-Pollack's brain puncture, but also to angio- and encephalography. We are recording in this paper three cases of Pick's disease diagnosed during life, each presenting peculiar arteriographic and ventriculo-encephalographic features.

CASE REPORT.

Case 1.—S. S., female, aged 57, was under observation in the University Neurological and Mental Hospital, Budapest, from May to June 7, 1938. *Family history:* Her father had two apoplectic fits with subsequent "insanity" and died at the age of 37. Her mother is said to have suffered from melancholia and died in hospital at the age of 60. A sister of her mother died "insane" at 70; a brother committed suicide at 50. *Personal history:* Climacteric five years before admission. During the last year the patient had become exceedingly absent-minded, being unable to do her housework, to cook or to take charge of money. During the week preceding her admission she showed some mental excitement. *Neurological examination:* The pupils were of average size, equal and regular, reacting normally to light and on accommodation. The other cranial nerves were normal. There were senile changes in the fundus. All tendon, periosteal and skin reflexes were normal. There were no pathological reflexes and no trace of clonus. The naso-oral and naso-mental reflexes were well-marked. Grasping and groping phenomena were present on both sides, more especially the right. Apart from these signs there were no motor or sensory disturbances.

The area of cardiac dullness and the heart sounds were normal; the pulse regular, the blood-pressure 115/75 mm. *Laboratory examinations:* Urine normal: Wasserman test in blood and cerebrospinal fluid negative. Cell count in the cerebrospinal 0, total albumin 17 mgm. per cent., the globulin reactions as well as the various colloidal reactions normal. *Mental findings:* *Speech:* was normal except for slight articulatory uncertainty with difficult test-phrases; there was, however, no definite dysarthria. Reading, writing, copying and drawing showed no noteworthy defect. There was no evidence of aphasia, apraxia or agnosia. She was uncritical, apathetic and devoid of initiative, remaining inactive throughout the day or else following passively the example of her fellow patients. She could comprehend simple commands, but complicated orders presented serious difficulties. Her attention was much impaired; she failed entirely in Bourdon's test, and showed a marked inability to attend to stimuli. *Memory:* while she had retained engrams of older date, she was incapable of remembering a date or a name given her a few seconds before, if her attention had been diverted for a moment, even though she had been warned to concentrate on the test. She could repeat immediately twelve syllables or four digits, but was unable to remember two digits after her attention had been distracted for a second. There was no confabulation. Her consciousness was unimpaired, the autopsychic orientation as well as the orientation in space was good. She was, however, completely disoriented in time, and was unable to say whether she had been in the hospital for a day, a week, or a month, what was the season, the day or

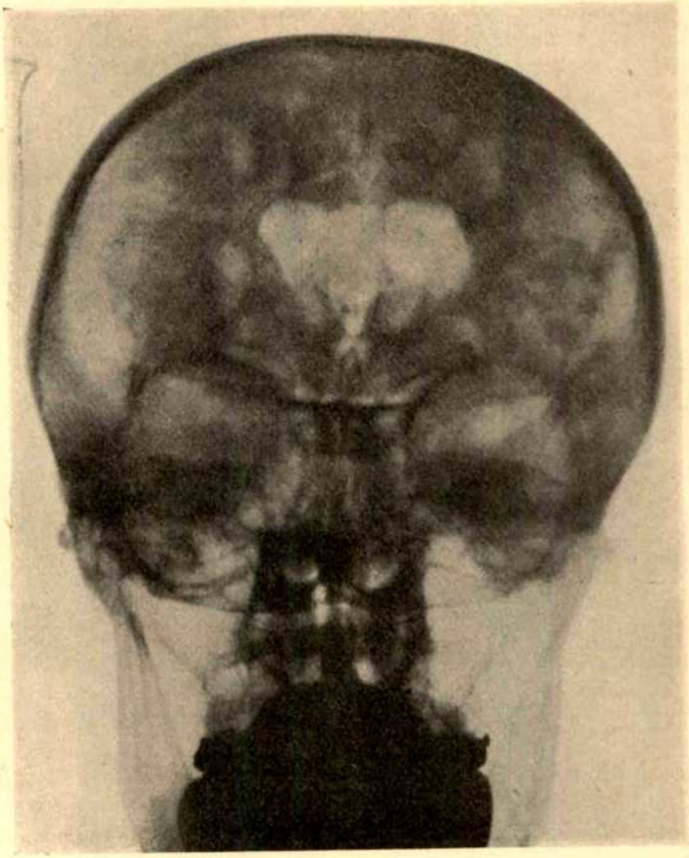

FIG. 1.

the time of the day. Her association was slow, poor and unproductive. There were no delusions. Her intelligence showed an uneven but grave impairment. Binet-Simon tests gave an age of nine years. Emotionally she was responsive, and affectionate towards her relatives.

Encephalography (50 c.c. air were introduced by suboccipital and 30 c.c. by lumbar puncture): the anteroposterior picture showed very dilated anterior horns, without, however, any abnormal configuration. The cavum septi pellucidi was enormously dilated (fig. 1). Radiograms taken two days later showed that the air had passed from the cavum septi pellucidi to the lateral horns, the 5th ventricle had disappeared and the anterior horns had become considerably wider. The lateral ventricles and the posterior horns were also very much dilated. Quantities of air were present in the subarachnoid spaces especially around the poles and the convexities of the frontal lobe, and less markedly around the temporal and occipital lobes (fig. 2). The intergyral spaces were unduly wide, and ribbon-like, uniting in cystic confluences. After the suboccipital injection of 2 c.c. of *lipiodol ascendant* the opaque oil settled mostly in the cisterna chiasmatis, a few drops, however, passing into the lateral ventricles.

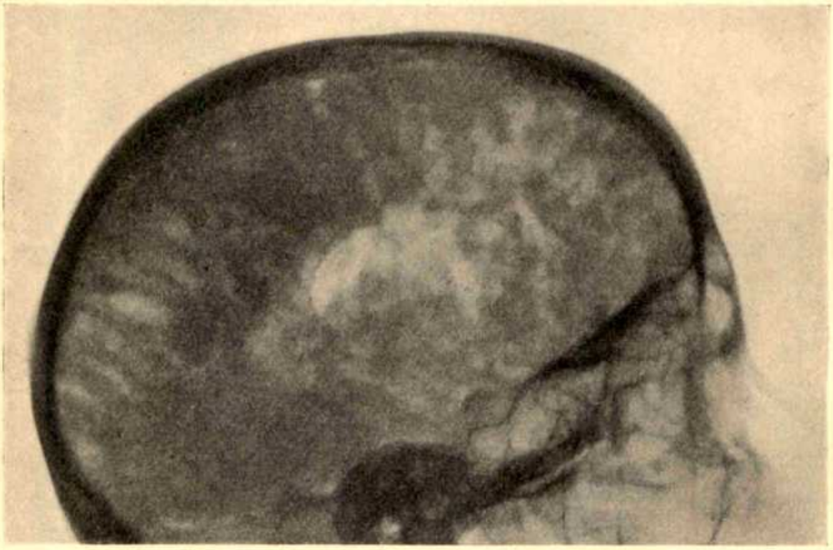

FIG. 2.

Course.—During the four weeks of the patient's stay in the hospital her condition became steadily worse. She became unable to find the lavatory, or to get back from there to the ward. Spontaneous grasping occurred on both sides, but more pronouncedly on the right. There was adiadochokinesis in the right arm. The patient's attitude, day by day, was that of an increasing apathy and dementia. She was unable to copy any of *Goldstein-Katz's* figures even if they were left before her. In most instances she wanted to draw her own sketch on the corresponding figure, but gave up the task helplessly after a few meaningless lines. Her failure to recognize the pictures, or to match them with other objects, demonstrated the patient's incapacity to deal with abstractions. She said spontaneously of the figure:—

"This is a triangle, is it not?" This shows that she could recognize the fact that it was a geometric figure but was unable to classify it. Of another linear figure Λ she said: "Quadrangle, is it not?" Her utterances always betrayed perfect helplessness which was also manifest in the repetition of the questions. In two instances we administered a tablet of benzedrine; thereafter the patient became restless and walked up and down the corridor completely disorientated.

Clinical summary.—The patient presented intellectual deterioration beginning at 52 and progressing during the following five years, characterized by a lack of initiative, apathy, impairment of perception and of the reception and retention of engrams, of the critical faculties and an inability to form abstractions. The neurological findings were: naso-oral and naso-mental reflexes positive, forced grasping on the right side. Encephalogram: enormously distended ventricles, wide intergyral cavities presenting a strip-like aspect with cystic confluences, especially over the frontal region.

Case 2.—A. B., female, aged 50, was under observation in the University Neurological and Mental Hospital, Budapest, from January 29, 1937, to April 23, 1937. *Family history:* Her father died at the age of 75; in the last years of his life he was markedly senile. *Personal history:* during the two years preceding her admission the patient was forgetful; she neglected her household duties, complained that she was not to be trusted with anything . . . "that she was like an idiot."

Neurological examination.—The optic fundi and cranial nerves were normal; the pupils reacted well to direct and consensual light and on accommodation. There was a slight tremor of the eyelids. The tendon, periosteal and superficial reflexes were normal. There were no pathological reflexes and no clonus. There was no grasping, groping, sucking reflex or "Gegenhalten." There were no motor or sensory disturbances.

Mental examination.—The patient understood words well, her attention, however, was often defective. In spontaneous speech she had difficulty in finding the words; in reading long words she hesitated and omitted syllables. In writing the same features were apparent. She was unable to recognize or reproduce numbers of three or more digits. There was no aphasia, agnosia or apraxia. According to her husband, her handwriting had deteriorated. Her behaviour was characterized by a lack of spontaneity. Usually she lay in bed, or sat in one place without stirring. She displayed no interest in her surroundings. Her spontaneous activities were limited to the more necessary actions, such as going out to the lavatory or for her meals. She was apathetic, but open to emotional approaches, liked her home, was glad to see her husband and talked willingly about her children. Her attention was affected; she could not concentrate on a subject even for a few seconds. She was unable to carry out double or triple commands. She could respond to stimuli from without only with great difficulty. Because of the serious defect of attention her ability to receive engrams could not be examined by means of the usual clinical tests. Her reproductive memory was defective but improved on repeated and energetic questioning; indicating a state of pseudodementia. Her orientation in space, on the whole, was retained, while in time she was totally disorientated. Her insight into her condition varied; at times she felt that she was healthy, at other times she complained of forgetfulness.

Physical examination and the laboratory investigations revealed nothing abnormal. In particular the cardiovascular system was intact. The blood pressure was 125/95 mm. The Wassermann test in blood and cerebrospinal fluid was negative, and the colloidal and globulin reactions in the fluid were perfectly normal.

Encephalography.—25 c.c. of air were introduced suboccipitally: the right lateral ventricle was slightly but evenly dilated while the left lateral ventricle, on the whole, was of a normal configuration. The subarachnoid spaces were much dilated over both frontal lobes, especially over the polar and orbital surfaces.

Cerebral arteriography with 25 per cent. thorotrast solution showed conspicuous changes in the configuration of the anterior cerebral artery (fig. 3). Its pericallosal branch showed a changed course from its origin in the upper curve of the carotid syphon. Instead of passing upward and forward in a wide curve corresponding to the convexity of the genu and body of the corpus callosum, it turned up and backward only after having crossed the double projection of the pars orbitalis of the frontal bone. The A. pericallosa marginalis also originated in the upper curve of the carotid syphon, and ran obliquely forward and upward crossing the pericallosal artery in an unusual fashion. It may therefore be assumed that there was a considerable atrophy of the frontal part of the corpus callosum which deprived the anterior cerebral artery of its support and so resulted in undulations in its course instead of the usual spanned arch. The part corresponding with the genu was straight and steep. In the first part of the A. pericallosa marginalis there were deep and sharp breaks due to the severe atrophy of the convolutions and the separation of the sulci. A similar deep and sharp break was to be observed in the external orbitofrontal artery and the perolandic artery and on the prefrontal artery. The topography of the Sylvian group of vessels presented, on the whole, a normal

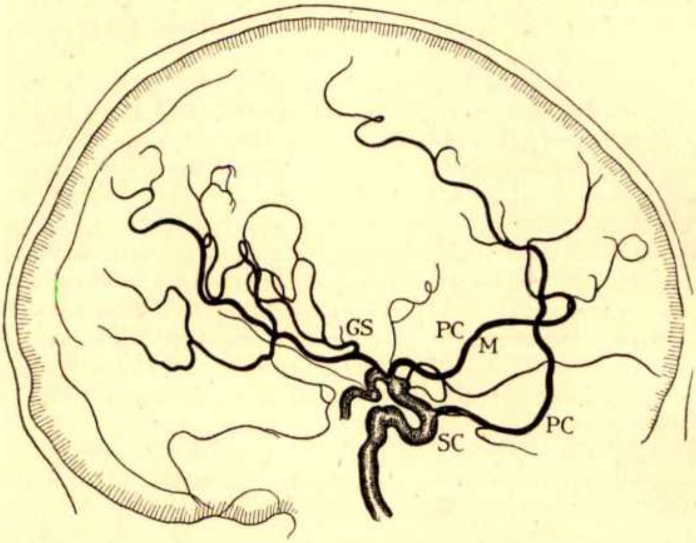

FIG. 3.—GS = Sylvian Group, SC = Carotid Syphon, PCM = Art. Pericalloso-marginalis, PC = Art. Pericallosa.

picture. There were considerable changes in the carotid syphon. The upper curve was obviously compressed and pushed downward, and the final part of the carotid, forming the upper branch, was flattened. This may be explained by the fact that owing to the atrophy of the frontal lobes the subarachnoid spaces became distended and their increased cerebrospinal fluid contents exerted pressure upon the carotid syphon, the more so as the cisterna chiasmatis and the lamina cinerea terminalis shared the increased local pressure.

Brain puncture was carried out by the Neisser-Pollak technique.—Brain cylinders containing the 1st, 2nd and 3rd cellular layers of the frontal cortex were stained by Nissl's method. All the nerve cells were pathological, the majority showing honeycomb-like degeneration. Fatty degeneration and to a lesser extent homogenous sclerosis were revealed by fat stains. The glia participated actively in the process of the demolition of the fats ; in the white matter there was an increase of glia. A silver impregnation stain showed small argentophil senile plaques scattered throughout the cortex. There were no Alzheimer's fibrillary changes. Here and there the axons showed evidences of degeneration.

Course.—After the brain puncture there were signs of meningeal irritation with fever, rigidity of the neck, Kernig and Brudzinsky's signs. There followed a rapid deterioration in the patient's condition. Her attention became even more impaired and her answers inadequate ; she displayed a demented euphoria. She sang much during the day and laughed stupidly. The neurological findings remained negative.

Clinical summary.—An intellectual disintegration, starting at the age of 48 years, proceeding slowly, characterized by a lack of spontaneity, a grave impairment of the reception of engrams, complete disorientation in time, loss of higher productive intellectual processes, limitation of the mental horizon and of the capacity for attention. The encephalogram showed extensive atrophy of the frontal lobes. Angiographically it was possible to demonstrate atrophy of the frontal region and of the corresponding parts of the corpus callosum.

Case 3.—B. I., aged 61, female, was under observation in the University Neurological and Mental Hospital, Budapest, from November 20, 1937, to July 9, 1938. No *family history* was obtainable. *Personal history*: Climacteric at 48, followed by periods of excitement for two years. At 56 she became gradually more and more restless. This phase was followed in the two years preceding her admission by a gradual lack of spontaneity, disturbance of speech, and depression, later by dementia. Four days before her admission she lost her way in the street.

Neurological examination.—The fundi were normal. The cranial nerves showed no abnormality. The pupils reacted promptly to direct and consensual light, as well as on accommodation, but with a small excursion. Motor symptoms: gait was normal but slightly stooping. The tendon reflexes were increased and the naso-oral and naso-mental reflexes easily elicited. There were no signs of a pyramidal or extra-pyramidal lesion, no tonic neck reflexes, no abnormal postural reflexes, no " Stützreaktion " (extensor thrust), no "*Gegenhalten*," no grasping or sucking reflexes. Sensation was intact and there was no disorder in any of the special senses.

Mental examination.—The psychological picture was dominated by a grave disturbance of speech. She could not understand questions nor speak spontaneously, although she was capable of phonation. She had also lost her ability to write, read, repeat after hearing, as well as to copy writing or drawings. She was equally at a loss with written as well as oral direction. Whatever the demand, she wrote when given a pencil a capital B followed by stereotyped illegible lines in the likeness of a signature. At times she could utter a few short words like "Yes" or "No"; the rest of her speech was unintelligible. It must be emphasized that the patient was not mute, for when alone she murmured incomprehensible fragments of words. The only means of communicating with her was by way of gestures. At times she was able to perform required tasks by imitation. She understood the significance of a hand being reached out to her; she could be induced with suitable gestures to undress; she even assisted in attending to the patients. In all her actions there was a conspicuous tendency to perseveration. Movement once begun was continued even when it had become unnecessary. At times she confused different objects and tried to use a comb for a toothbrush. There is justification therefore for diagnosing an ideomotor apraxia. She could repeat songs, or sing quite correctly in unison, pronouncing the text also; how-

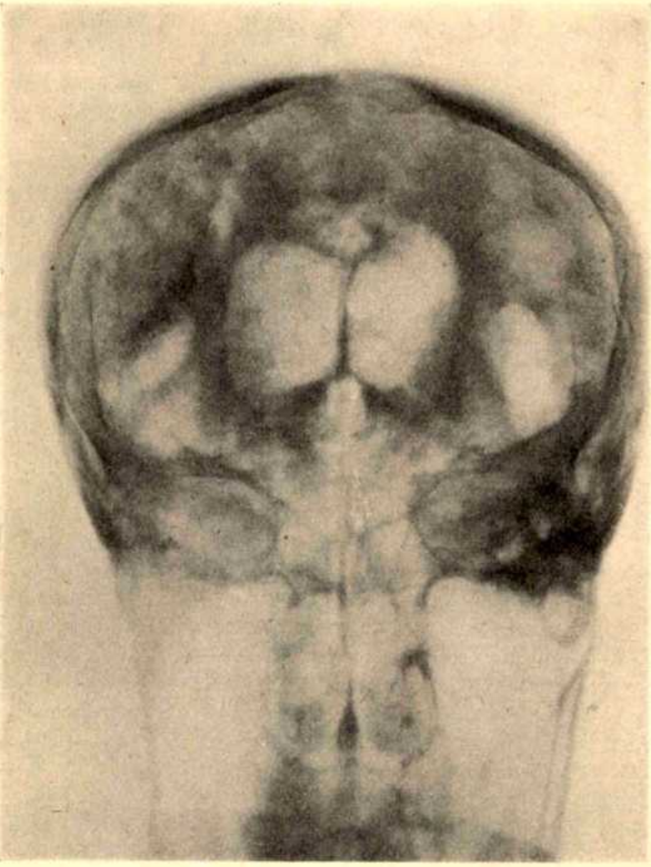

FIG. 4.

ever, she could never repeat the text alone. Her behaviour was quiet and composed. She sat all day quietly, with an utter lack of spontaneity and initiative. Her attention was relatively good as shown by emotional responses and her ability to imitate. She watched her companions and joined them in their occupations. An exact examination of attention, however, was just as impossible as that of perception, memory, intelligence and orientation, because of the great incomprehension of words. Emotionally she was approachable; she was glad to see her relatives, and understood expressions of pleasure and anger. She was unable to solve any of the Herderschee tests for the examination of deaf-mute children. She could not comprehend the simplest tasks.

Physical examination showed nothing abnormal. The cardio-vascular system was intact; the blood pressure 175/80 Hg mm. Wassermann test in the blood and the cerebrospinal fluid was negative, the cell count in the fluid was 5/3, the albumin content 20 mgm.%; chlorides 0·6%; all colloidal reactions normal; globulin reactions negative. The urine was normal.

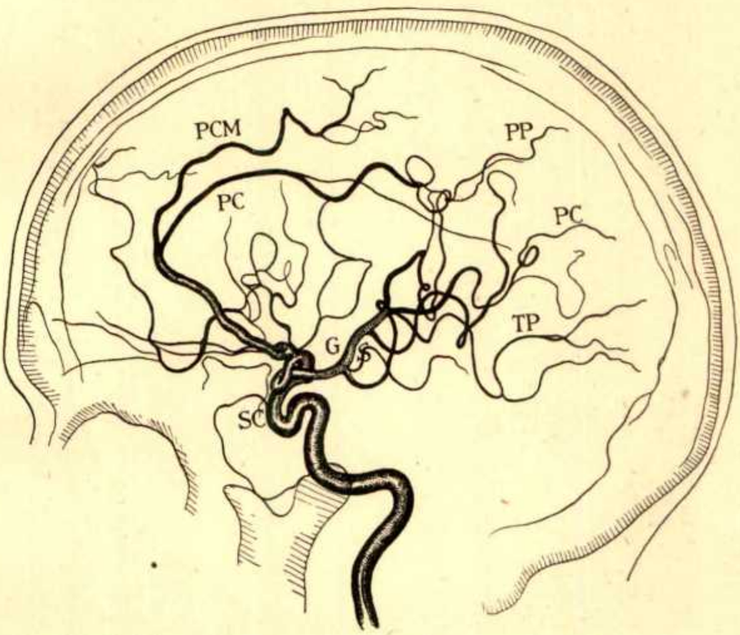

FIG. 5.—GS = Sylvian Group, SC = Carotid Syphon, PCM = Art. Pericalloso-marginalis, PC = Art. Pericallosa, PP = Art. Pariet. Post., TP = Art. Temporalis Post.

Encephalography (80 c.c. air suboccipitally, 30 c.c. by lumbar puncture).—The ventricle showed a considerable generalized dilatation (fig. 4). The intergyral cavities of the frontal and temporal and to a lesser extent of the parietal region appeared on account of the extensive atrophy as round or longish, ribbon- or cyst-like formations. Especially conspicuous were two larger cysts formed by confluent small cavities on the lower and lateral part of each frontal lobe, corresponding with the frontal opercula.

Arteriography.—The paracentral and posterior part of the left pericallosal artery was slightly undulating ; at the same place the pericallosal marginalis showed sharper angulation (fig. 5). Traces of the same feature were visible on the posterior temporal artery and the so-called artery of the angular gyrus. The wide curve of the right pericallosal artery was interrupted at a right angle. The carotid syphon showed no considerable changes.

Brain puncture by Neisser-Pollack's method.—In material obtained from the frontal region the pyramidal cells of the cortex were either finely vacuolar (honeycomb-like degeneration), or swollen with homogenous sclerosis (dark cell plasm, pyknotic, angular nucleus). At times there were cell-shadows. The glial nuclei were mostly light in colour and slighty swollen with hypermetachromatic granules around the nucleus (fig. 6).

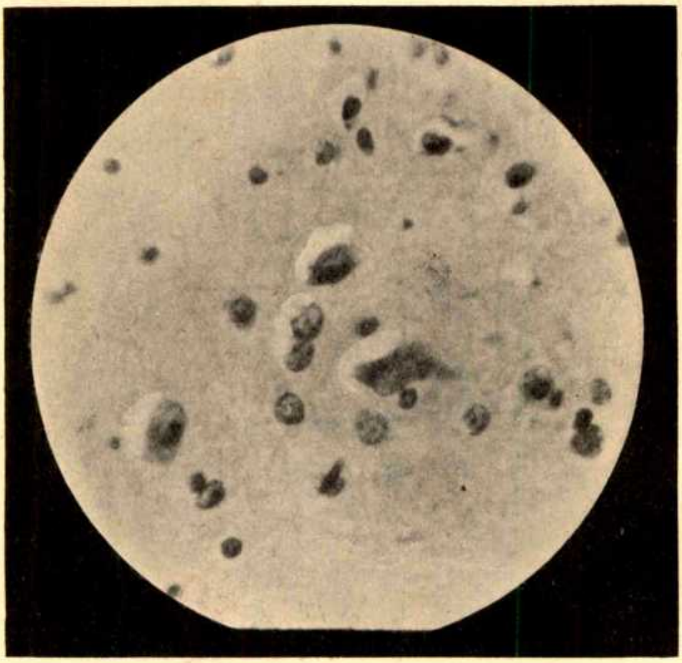

FIG. 6.—*Case 3.* Photomicrograph showing tissue obtained by brain puncture. Nissl's stain ; × 585. The nerve cells show the pathological alterations demonstrated on fig. 11. The glial nuclei are light, swollen (active phase).

Course.—The encephalography was repeated at intervals of four to six weeks with identical quantities of air, the patient tolerating all interventions well. *The large opercular cyst visible in the anteroposterior views became in subsequent pictures not only larger and higher, especially on the left side, but also different in shape, i.e. irregularly elliptical instead of triangular as before.* For a more exact picture of the ventricular system *ventriculography* with simultaneous brain puncture was performed on June 8, 1938. The ventricles were considerably dilated. The anteroposterior views showed an abnormal dilatation of the left anterior horn (fig. 7). This was still more evident in the lateral views (fig. 8) which also showed an extraordinary dilatation of the frontal horn. This with a steep hump-like outline to the upper limit of the anterior horn produced a strange asymmetrical club or dumb-bell appearance. The apex of this protuberance approached in the direction of the cranium the projection of the lamina vitrea. The centre of the arch was projected on the picture immediately below the upper contour of the smaller right frontal horn. Behind the massa intermedia of the 3rd ventricle there was a defect of filling as thick as a pencil, through the trigonum down to the temporal horn. This defect was formed by the glomus chorioideum. These appearances were to a lesser extent visible in the right lateral ventricle. The postero-anterior picture was in correspondence with these findings. After the ventriculography and the brain puncture the patient developed a subnormal temperature (37·9° C.) with weakness and pronounced meningeal signs. At the same time there was asymbolia for pain. The patient showed no evidence of pain or defensive reactions in spite of the intense meningeal symptoms. Later there was a gradual deterioration; she became totally indifferent, emotionally less approachable; her spontaneous speech became still worse; even her "yes" and "no" disappeared. She was unable to walk; kept her lower extremities

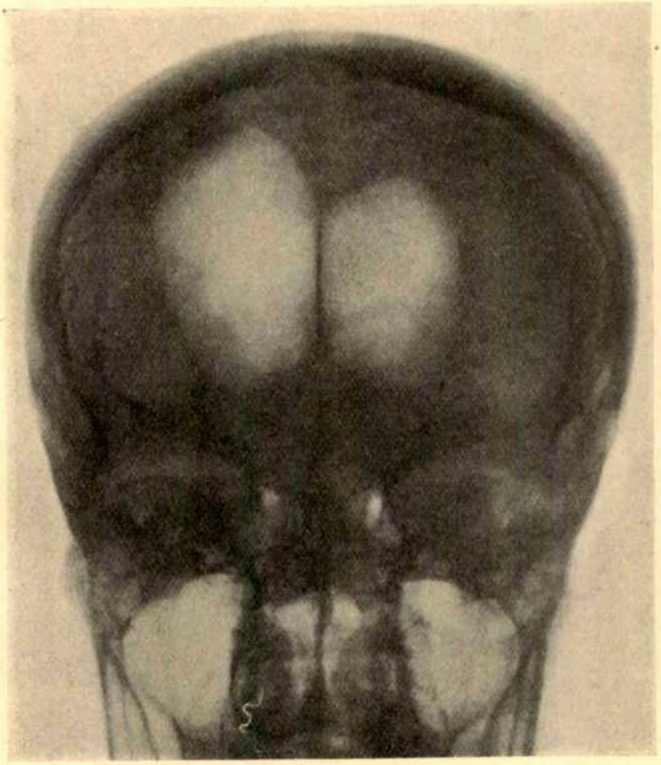

FIG. 7.

bent at the knee and fell sideways if made to sit up. Even in this condition she was at times able to repeat to some extent texts which were sung to her. The naso-oral and naso-mental reflexes could now too be elicited. There were no other abnormal reflexes or pyramidal signs and no evidence of paresis.

Clinical summary.—A pathological process of five years' duration beginning at the age of 56, characterized by a lack of initiative and spontaneity, a tendency towards imitation (echopraxia), relative emotional and attentive accessibility, grave disturbance of speech (sub-total aphasia), with the ability to repeat refrains ("echomusia"). The naso-oral and naso-mental reflexes well marked. She was unable to pass any of the tests designed for the examination of deaf-mute children.

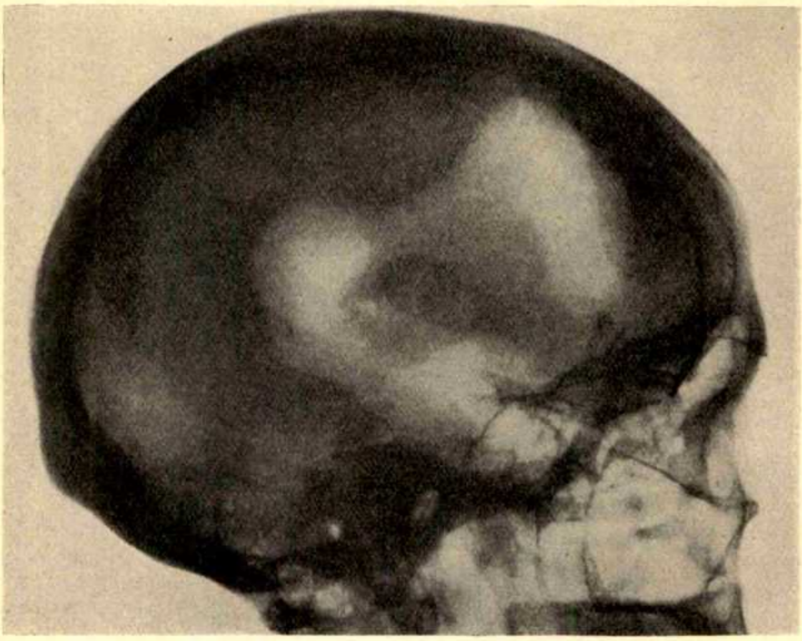

FIG. 8.

The considerable amount of air visible in the encephalographic picture over the fronto-temporal and to a lesser extent over the parietal region demonstrated the severe atrophy of the cerebral cortex. The profound disturbance of speech was associated with the bilateral, but asymmetrical opercular cysts which proved by repeated encephalograms to be growing more and more extensive. The ventriculogram showed a peculiar configuration of the ventricles, being dumb-bell in shape, with the narrow connecting part corresponding to the central part of the lateral ventricle. The anterior and posterior horns were considerably dilated, especially on the left side; the left inferior horn was also increased in size. The arteriogram showed changes indicating cerebral atrophy. The nerve cells in the material obtained by brain puncture showed pathological changes. The meningeal reaction after the brain puncture caused a rapid aggravation of the intellectual deterioration.

Diagnosis.—In the differential diagnosis of the three cases it was important to exclude brain tumour, general paralysis, cerebral arteriosclerosis and senile dementia. All these were eliminated by our clinical and laboratory data.

We should like to consider more carefully the differential diagnosis from Alzheimer's disease, made possible by the following finer clinical symptoms:

In all three cases, in spite of small qualitative and quantitative differences, there was a characteristic form of dementia. In spite of the grave intellectual deterioration, and the serious impairment of the critical faculties, we found in all the three cases an emotional accessibility.

Our first patient was always glad to see her relatives and wanted to go home with them. The attention of the second patient could also be held though only for a while by questions of an emotional content, e.g. regarding her sons. The third patient readily betrayed emotional responses. Both in Case 1 and in Case 3 there was a well-preserved emotional response. These observations are in harmony with those of v. Braunmühl (1934), Stertz (1926) and Schneider (1927), according to whom there does not occur in Pick's disease a complete loss of the mnestic associative functions as in Alzheimer's disease.

As for the general mental attitude, the first two patients, who represented earlier phases of the disease, displayed in a clear fashion the traits said to be characteristic by Goldstein and Katz (1937): "the active abstract attitude in behaviour is lacking, whereas the concrete type of behaviour is relatively well preserved." This was a helpful point in excluding the diagnosis of Alzheimer's disease.

It may be said of the disorder of memory that the most conspicuous element was the almost complete lack of receptive memory. The first patient was unable to repeat the date given a few seconds before; the second was often unable to repeat words immediately. The third patient could not be examined in this respect on account of her aphasia. According to Stertz the cause of this defect is the lack of tenacity of attention, the great distractability of the latter, while according to Goldstein and Katz the cause is to be sought in the inability of the patient to choose between different stimuli. In Case 1 the latter hypothesis seems improbable because the patient also failed if she received no further stimuli in the short interval required for the experiment. With Case 2 the impairment of the receptive memory seemed to be secondary. It was to be explained by the patient's difficulty in applying herself to the actual stimulus. Whatever the cause, it is undeniable that one has to deal with a grave disturbance of the receptive and retentive memory only, differing from Alzheimer's disease, where the disturbance involves *all* processes of memory. In view of these facts we cannot share Nichol's and Weigner's (1938) opinion. According to these authors it is "not so much memory itself that is lost but rather the use of it in the formation of new ideational material." In our cases, however, there were conspicuous disturbances of receptive and retentive memory, although there was also a "loss of memory as a tool" in Kahn and Thompson's sense.

J. Ley (1935), and Ferraro and Jervis (1936) have suggested other clinical symptoms useful in distinguishing between the two diseases. Of these some are characteristic of Pick's disease, such as anxiety, depression, logoclonia, palilalia and epileptiform seizures. These were lacking in all our three cases. In Case 3 we noted echolalia and echopraxia—said to be characteristic of Pick's disease (Grasse (1934), Ferraro and Jervis (1936)). In all the three cases the patients were apathetic, with expressionless faces ; there were no concrete psychotic symptoms ; there was no insight into the disease and no pronounced motor disturbances such as paresis or tremor.

From these clinical characteristics we doubtless had to deal with Pick's disease in all three cases. It also indicates that the clinical syndrome as a whole in Kahn and Thompson's (1934) sense may actually be utilized in differential diagnosis.

Encephalo- and arteriography.—We have pointed out elsewhere that though these procedures carefully employed are a great help to the neurologist it would not be desirable were they to attain an undue importance over the clinical findings, thus making the clinical neurological diagnosis a mechanical procedure.

Pneumoencephalic pictures have been utilized by several authors (Lemke (1934), Benedek and Horányi (1937), Nichols and Weigner (1938), and others) for the corroboration of the diagnosis of Pick's atrophy. According to the variants of Pick's disease we may expect either a distension of the anterior horn—in the case of the circumscribed atrophy of the frontal lobe, or a dilatation of the anterior horn, the trigonum and the base of the occipital horn, as in the case of temporal forms. In the isolated lobar destruction of the parietal part we may expect destruction of the cella media, the pars descendens and the vestibular region as well as of the projection of the posterior horn.

(*a*) Our encephalographic pictures showed the symmetrical subarachnoidal air-filling characteristic of Pick's disease: in Case 1 especially over the frontal pole and the convexity, to a lesser extent over the temporal and occipital lobes (fig. 2) ; in Case 2 on the polar and orbital surfaces of the frontal lobes; in Case 3 over the frontal and temporal, to a lesser extent over the parietal regions. The air, visible in the form of ribbon-like stripes, spots or small cysts, was localized to certain regions of the brain and *not diffuse* as in Alzheimer's disease (Flügel (1932)).

A special picture is presented by Case 3, where the above mentioned stripes and spots constitute on both sides, but more especially on the left, large cystic formations over the frontal opercular region (fig. 4). This adequately accounts for the grave disturbance of speech. Richter (1918) also found a marked atrophy of Broca's area involving also the orbital gyri. As the encephalography was repeated five times in Case 3 at intervals of four to six weeks, we had a unique opportunity for observing the development of the atrophy of the brain: the opercular cyst appeared, especially on the left side, considerably wider at each subsequent examination. This is in agreement with the aggravation of the aphasia within the last two months of clinical observation.

The ventricular system showed the least changes in Case 2 where there was a uniform distension; in Case 1 the cavum septi pellucidi was visible between the considerably dilated anterior horns (fig. 1). Pictures made two days later no longer showed this formation, and the anterior horns, especially on the left side, were much wider. The other parts of the ventricular system were evenly distended without any peculiarities. An unusual picture was presented by the ventriculograms of Case 3. The ventricular system was greatly dilated. We should like to emphasize the irregularity of this dilatation. Both anterior horns, especially the left, were so enormously distended that they approached within 1 cm. the projection of the lamina vitrea of the calvaria, and downwards the orbital part of the basis of the cranium (fig. 7). The lateral picture showed the anterior horns enormously dilated. The upper contour showed a hump-like protuberance, the centre of the left curve of which was immediately below the upper contour of the smaller right frontal horn. The posterior horn was again much distended, and of a peculiar spherical shape. It passed without any narrowing to the inferior horn which again was enormously wide, especially on the left side (fig. 8). The atrophy was more pronounced on the left. This phenomenon is known to be present in Pick's disease and can be explained by right-handedness. The lateral ventricles accordingly presented a peculiar dumb-bell or club-like shape to be attributed to the relative sparing of the central parts. It should be mentioned that the central part is known to be affected in some cases.

Different parts of the ventricular system present certain slight variations of form though within physiological limits. According to our experience it is especially the posterior horn that varies. The least variable of the different parts of the lateral ventricles is the anterior horn.

The radiological diagnosis of Pick's disease is therefore not absolute. The use of encephalo- and ventriculography is becoming more and more important with the improvement in technique. In our observations also we obtained data regarding the progressive increase in the atrophy which have not been obtained before during life.

(*b*) The vascular topography may present individual normal variations. Characteristic in this respect is the " formation of knots " as seen in the stereo-angiographic pictures. These facts indicate the necessity of considering the arteriographic findings in conjunction with the radiograms and encephalograms as well as with the clinical findings.

The angioarchitectonic structure may be affected in other ways by atrophic processes of the cerebral parenchyma. The arterial branches may show unusual angulations corresponding with the thinning of the gyri. Instead of a slightly undulating line we may be confronted with a series of sharp bends. This can be observed in our Case 3 (fig. 5), but especially in Case 2 (fig. 3) where there appears a forward and downward deviation of the pericallosal artery and a compression of the carotid syphon. We ascribed these phenomena to an atrophy of the frontal lobes and of the corpus callosum. In a more severe cystic atrophy it is possible that the artery no longer follows the surface of the atrophic gyrus, but remains spanned over the sulcus. At such times the irregular undulations of the arteries are replaced by straight lines or wide arches formed by rigid blood vessels. This can be seen in Case 2 and to a lesser extent in Case 3. A similar appearance was shown in one of our cases of disseminated sclerosis with considerable cortical atrophy where the angiographic features were confirmed at autopsy. In this case the blood vessels were straightened, especially in the territory of the anterior cerebral artery. It was interesting to observe in stereoscopic angiograms that the level of the polygon formed by the pericallosal and the pericallosa-marginalis vessels formed an oblique angle towards the corresponding hemisphere on account of the atrophy of the cortex. In other cases the arterial systems deprived of their support may be dislocated and form unusual crossings as in Case 3 (fig. 5). The destruction of the nerve substance, the shrinkage of the supporting tissues and the regressive hyaline and fibrotic changes in the walls of the blood-vessels, produced in our cases of general paralysis a fairly characteristic though scarcely a pathognomonic stereo-arteriographic picture: rigidity of the arterial stems, discontinuity of the terminal branches and an arterial network devoid of detail. In a case of amyotrophic lateral sclerosis with bulbar involvement there were psychological symptoms suggesting extensive cortical atrophy. Our angiograms here too showed the well-known changes, the sharp breaks and saddle-like hollows in the pericallosal artery, the compression of the right carotid syphon, the conspicuous thinning of the pericallosal-marginalis and of Duret's internal frontal arteries.

Neisser-Pollack's internal brain puncture.—Cylinders obtained by brain puncture in Cases 2 and 3 showed extensive and marked changes in the frontal cortex: mostly honeycomb-like degeneration with evidence in appropriately stained specimens of fatty degeneration, and to a lesser extent homogeneous sclerosis (fig. 6). The glia took an active part in the process of fat dissolution. The glial nuclei were light and were surrounded by hyperchromic granules. In Case 2 it was possible to demonstrate by the Bielschowsky impregnation method small incipient senile plaques consisting of amorphous argentophil areas with no concentric or radial structure. There were no Alzheimer fibrillary changes. The axons showed at certain places degenerative changes both in the cortex and in the medullary substance. These changes afforded also a histological proof of the severe affection of the cerebral region in question. In the literature of the subject only in Lemke's case was the diagnosis confirmed by brain puncture.

It is noteworthy that in both cases the brain puncture was followed by a meningeal reaction which in its turn resulted in an increased activity of the fundamental process.

Neurological changes.—In Case 1 there was a somewhat sluggish reaction of the pupils, senile changes in the fundus, grasping and groping (more on the right side) which later became more obvious during the month while the patient was under observation. This frontal symptom is rare, according to Schneider (1927), and occurs only in slowly progressive cases. In Case 1 and Case 3 there was a very pronounced naso-oral and naso-mental reflex; these have not been mentioned before in the literature of Pick's disease.

Schmitz and Meyer (1933) have described a reaction which consists of opening the mouth when any object is held in front of it. Neither this, nor swallowing, licking, chewing or sucking reflexes were observed in our cases.

In all the three cases the frontal syndrome was represented above all by mental symptoms, by a lack of impetus and of spontaneity, and by disturbances of volitional initiative.

The speech of our second patient showed a change inasmuch as the association of ideas with the corresponding names was affected; the "symbolic function" (Head) was disturbed in its motor aspect.

The disturbance of speech in Case 3 was a total aphasia with the difference that though the patient failed—as in the other tests—in the repetition of phrases, she could sing a text faultlessly with the examining physician. This symptom occurs chiefly in motor aphasia. The only observation similar to ours has been made by Schmitz and Meyer, with the difference that their patient did not speak for weeks. *We propose to call the symptom echomusia.* In its causation a certain rôle may be played by the emotional accessibility of the patient, for, as the patient became emotionally duller the echomusia also became less evident. In this case we also found echolalia and echopraxia, at times palilalia (Grasse).

In Case 1 as in Rosenfeld (1909) and Heilbronner's (1900) case, there were no disturbances of speech.

Apraxia, agraphia, alexia, acalculia were absent in Cases 1 and 2, the minor disorders of action, writing, reading and counting being due to the disturbances of higher functions. The second patient, for instance, could read long words only by scanning each syllable, starting again and again; she was unable to write down numbers of more than one digit because of the disturbance of receptive memory.

In all the cases the tonic neck reflexes, the postural reflexes, Magnus' supporting reaction, disturbance of standing and gait were absent. In Case 3, during the mental deterioration following the brain puncture and ventriculography, total astasia and abasia appeared and lasted for four weeks, although the meningeal symptoms cleared up earlier, and there were no pyramidal symptoms. No extra-pyramidal symptoms were observed differently from van Bogaert's case. We may mention here the opinion of Critchley (1931) that some of the neurological symptoms in elderly patients are due to lesions of the basal ganglia.

Heredity. Gans (1922), and Onari and Spatz (1926) considered the possibility of the phylo- and ontogenetically youngest and therefore most vulnerable frontal regions, especially Brodmann's areas 43 and 46, being first involved in the atrophy. Later Richter (1918) emphasized the heredodegenerative character of the illness. There have since been extensive investigations regarding the genetic circumstances of the cases. The familial character of the disease is proved by data established by Fischer (1910, 1911), Benders (1915), Grünthal (1930), Haškovec (1934), v. Braunmühl and Leonhard (1934). Schmitz and Meyer's family tree also seems to prove the hereditary character of the disease. In opposition to these authors Moyano (1932) has recently denied the hereditary character of the affection. Only in one of Lowenberg's four cases were there hereditary trends. Guillain, Bertrand and Mollaret (1934) put forward the possibility of an infective origin. Ferraro and Jervis suggested a vascular origin (" we assume that vasomotor factors play a rôle in the pathogenesis of Pick's disease ").

In Case 1 there is indubitably a significant family history. The patient's father died at the age of 37 of a psychosis. His death is said to have been preceded by two fits of apoplexy. It is possible that the father was already suffering from Pick's disease and the fits of apoplexy were Stertz's (1926) seizures. Her mother also died of psychosis, at the age of 60. Nothing is known of her condition except that it was some kind of depression. In Case 2 there is a suspicion of the patient's father having died at an advanced age of senile dementia. Both in Cases 2 and 3, however, there are no clear heredofamilial data.

We think, from the data published in the literature, as well as from our own observations, the importance of heredofamilial factors may be taken as established.

SUMMARY.

(1) Three cases of Pick's disease all presented positive encephalographic findings. In two cases confirmatory evidence was obtained by brain puncture.

(2) The encephalogram showed in one case the 5th ventricle, in another extensive opercular cysts on both sides. A progressive increase in the size of these cysts was demonstrated by pictures taken successively at intervals of four to six weeks: the progress of the disease was thus encephalographically demonstrated.

(3) Cerebral angiograms showed changes attributable to the atrophy, such as compression of the carotid syphon, the curving forward and downward of the pericallosal artery, deep and sharp bends in several arterial branches. All these were more pronounced in Case 2 than in Case 3.

(4) Brain puncture demonstrated a severe degeneration of the frontal cells and axons, an activity of the glia, and in Case 2 incipient senile plaques.

(5) The ventriculogram of Case 3 presented a very unusual picture. The projection of the frontal horns of the lateral ventricles became enormously bulging, especially on the left side, thus giving the ventricular system a peculiar dumb-bell or club-like appearance.

(6) According to Schneider's (1927) classification, Cases 1 and 2 were transitional forms between Stage II and III, while Case 3 represented an early form of Stage III.

(7) On the basis of these three cases it may be asserted that the clinical-syndrome in itself is sufficient for the differential diagnosis of the disease.

(8) Of the clinical signs the following are noteworthy: In Case 1 the senile changes in the fundus and the grasping and groping; in Cases 1 and 3 the naso-oral and naso-mental reflexes; in Case 2 the transcortical aphasia, in Case 3 an almost complete aphasia. In the last case there were echolalia and echopraxia as well as a rare symptom we have called echomusia.

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NOTICES OF RECENT PUBLICATIONS.

Beitrag zur Kenntnis sklerosierender Entmarkungsprozesse im Gehirn, mit besonderer Berucksichtigung der diffusen Sklerose. By LARUS EINARSON *und* AXEL V. NEEL. Copenhagen: Einar Munksgaard. 1938. Pp. 160. Price Kr. 7.

This monograph is an attempt to classify the many cases of diffuse sclerosis of the brain and of Schilder's disease which have been published in the literature in the hope that such a classification might shed some light on the ætiology of the different groups. The difficulties surrounding this essay are obvious enough; not the least is the fact that many cases, which are published as isolated instances of the disease, have been shown by later observations to be familial. And there must be many other cases in which, for one reason or another, the familial nature of the disease is unrecognized.

Further, in interpreting the histological observations of various authors, their methods of examination and various other individual factors must be assessed. For example, the metachromatic prelipoids on which certain authors have laid emphasis may be invisible or almost so in sections stained by Weigert-Pal or hæmatoxylin-eosin methods. The authors have indeed recognized this difficulty as well as that inherent in the variations of stress which different authors place on different aspects of the disease.

On the basis of their survey of the literature and of their personal observations the authors classify diffuse sclerosis under:—

(1) The glioblastomatous form; (2) the exogenous inflammatory form or *leuco-encephalitis diffusa;* (3) the non-familial degenerative form; (4) the heredo-degenerative form or *leuco-encephalopathia progressiva hereditaria diffusa;* and (5) Balo's concentric sclerosis. Their third type is subdivided into (*a*) cases with mucoid degeneration of the oligodendroglia, and (*b*) cases which are characterized by the accumulation of metachromatic prelipoids in and round the demyelinated areas. Their fourth type is also subdivided into (*a*) the acute infantile type of Krabbe. (*b*) The subacute juvenile type of Scholz. (*c*) The adult type of Ferraro, and (*d*) the chronic type (infantile, late infantile and juvenile) which includes cases resembling the family described by Pelizaeus and Merzbacher.

For the most part this classification is acceptable enough. There are, however, some who consider that Balo's concentric type of demyelination lies nearer to disseminated than diffuse sclerosis. Nor is the blastomatous form of the disease generally accepted. The demyelinating effects of infiltration or pressure by a tumour, or of the œdema to which it may give rise, seem indeed to have been minimized or neglected by many of the authors who have described such cases, and it is therefore dangerous to accept their reports in an uncritical manner. Whether or not a transition form exists between tumour and diffuse sclerosis, linking the disease to tuberous sclerosis as the authors claim, is therefore doubtful.

The authors put forward many suggestions as to ætiology, most of which are old and are not supported by any stronger evidence than has been put forward in the past. The relationship of diffuse sclerosis in the human to cage paralysis in monkeys is lightly touched on, but no mention is made of "sway back" in lambs, which seems to be a closer and more fruitful analogy. The only new causative factor suggested is an insufficiency of vitamin E. This has been shown by Einarson to have some effect both on the nervous system and the musculature, and, on the basis of the more or less localized muscular wasting which often occurs in diffuse sclerosis, is put forward as a possible factor. No evidence is, however, advanced as to whether the muscular wasting is primary or is secondary to disease of the brain.

Taken as a whole, the monograph does little to increase our knowledge of diffuse sclerosis, although the new case records, especially Case I, are interesting.

Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN. Seventh Edition. London: Lewis and Co. 1938. Price 8s. 6d.

The appearance of the seventh edition of this useful handbook indicates its continued popularity. The section dealing with ventriculography has been amplified and new radiograms provided. In general its plan and contents remain as before

This work has perhaps not altogether escaped the dangers that beset the endeavour to keep successive editions up to date. The gradual accumulation of new matter tends to blur the original clarity and to overload the framework of the book, as well as to swell its bulk unnecessarily. There comes a time when sections thus amplified need to be recast. Only thus can obsolete and redundant matter be eliminated.

The necessity for such drastic recasting is well seen in the chapters dealing with the reflexes. For example, the student seeking to get information about the extensor type of plantar response: its receptive field under differing conditions, its motor field of response, its relation to the flexion reflex, and its behaviour in the extended and flexed forms of paraplegia no longer finds a continuous and coherent account. The two forms of paraplegia mentioned also need a more adequate description and interpretation than they receive

It is probable that future revision on these lines will again bring the book to that smaller original compass, the disappearance of which the author now deplores.

Comparative Anatomy and Physio-Pathology of the Autonomic Hypothalamic Centres. By A. A. BOON. Acta Psychiatrica et Neurologica, Supplementum XVIII. Haarlem: De Erven F. Bohn. 1938.

This timely and critical monograph sums up the present state of knowledge of its subject. The author concludes that important as is the hypothalamus in the regulation of vegetative and endocrine functions, its influence may be exaggerated. He cites the clinical observation that considerable lesions may be found in this structure in the absence of noteworthy vegetative disturbances. The bulbar and spinal vegetative centres may, up to a point, compensate for any loss of function the hypothalamus may suffer. On the other hand some hypophyseal and heat-regulating activities are strongly influenced by the hypothalamus, and cortical and striatal influences mediated by pathways from these regions to the bulbar and spinal centres have synapses in the hypothalamus.

Studies on Pain Conduction in the Trigeminal Nerve. By O. Sjöqvist. Acta Psychiatrica et Neurologica. Supplementum XVII. Helsingfors: Mercators Tryckeri. 1938.

The studies recorded in this monograph had as their starting point the practical end of devising a surgical means of abolishing the pain of trigeminal neuralgia without at the same time rendering face and cornea anæsthetic. Dandy had claimed that division of the posterior and inferior fibres of the 5th nerve sensory root near its point of emergence from the pons, produces a selective loss of pain sensibility in the face, but the observation had not been confirmed. Sjöqvist therefore undertook an anatomical study of the distribution of pain conducting fibres within the peripheral portion of the sensory root and also within its intramedullary and spinal portions. Starting with the assumption, for which he relates the relevant anatomical and physiological evidence, that the pain conducting fibres are the smallest, not exceeding 3 μ in diameter in paraffin sections, he traces their course within the central and peripheral portions of the sensory root. This process he speaks of as "fibre analysis." No qualitative grouping of pain fibres could be discovered in the peripheral sensory root of man, of a kind likely to make possible a dissociated anæsthesia by partial root section. But in the bulbospinal portion of the 5th nerve (in *Macacus rhesus* as well as in human material) the smallest fibres predominate, and section of this tract in human subjects of trigeminal neuralgia produced complete pain and temperature sense loss on the affected half of the face.

On the basis of this observation the operation of bulbospinal section for trigeminal neuralgia has been devised. The monograph contains full technical details of the operation, and records an admirably planned investigation with valuable practical results.

Theories of Sensation. By A. F. Rawdon-Smith. Cambridge University Press. 1938. Pp. 120. Price 10s. 6d.

The author gives the present state of knowledge and opinion on the functions of vision and audition, with special reference to the capacity to discriminate differences of amplitude and frequency in light and sound. This discrimination is of fundamental importance and its study throws light upon the wider problems of sensation. The electro-physiological researches of Adrian and his co-workers have extended our means of investigation in this field, and the bearings and promise of this line of research are fully discussed.

The Form and Functions of the Central Nervous System. By F. Tilney and H. A. Riley. London: H. K. Lewis and Co. Third Edition 1938. Pp. 789 and 600 figures. Price 50s. net.

When in 1921 the first edition of this work was noticed in these pages, the hope was expressed that later editions might contain a more adequate account of the physiology of the nervous system, and a terminology less luxuriant. These hopes have not been realized, and the present edition differs in no essential features from its predecessors. The name of Dejerine continues to be wrongly accented, and some of the figures to be attributed to the wrong authors, or not to have their source acknowledged at all. Thus figures 480 and 481 appear to be reproductions of Spalteholz's figures 710 and 711, while figure 397 attributed to Dejerine appears to be Spalteholz's figure 704 Errors of this order should not have survived into the third edition of a book.

But what is more important is the almost complete absence of mention of some of the major advances in the physiology of the nervous system of the past quarter of a century. The name of Magnus finds no mention and his researches and those of his school are unrepresented.

Where physiological functions are discussed the style is too often that of fifty years ago, when elaborate periphrasis and reiteration in vague abstract terms were the only available substitute for the physiological knowledge that was not then acquired. Thus the function of the Betz cells of the cortex is said to be to "transmit a part of the skilled motion formulæ" To speak of a cell transmitting a formula is not to use the language of science, nor indeed any language that has discoverable meaning, for cells do not transmit abstractions.

The discussion of cerebellar physiology is a striking example of a lavish use of abstract names that have no discoverable referents. Even where such a familiar phenomenon as Babinski's toe response is mentioned, no interpretation of it in terms of normal function is given, though the response has a considerable physiological interest.

It may be doubted, also, whether within the term "functions" of the nervous system a description of clinical syndromes of local lesions can be reasonably included. For these syndromes represent symptoms of lesions, and these are not the same as normal functions.

Nevertheless, despite these criticisms, the appearance of the third edition of this book indicates that in its present form it has been found of value to a number of readers, though of what category cannot easily be surmised, and if it is to continue in this form, a change of title that would warn the reader not to expect a statement of modern neurophysiology within its covers seems indicated.

Cranio-Cerebral Injuries. By Donald Munro. London: Oxford University Press. 1939. Pp. 393. Figs. 62. Price 21s.

Within the past twenty years the subject of intracranial tumour has dominated the literature of cranio-cerebral surgery in a measure out of all proportion to its importance. The books and original papers devoted to it are innumerable and ever increasing. They have been very fruitful in some respects. Thus they have shown the importance of a pathological diagnosis as an essential preliminary to operation, and they have recorded many new localizing symptom-complexes and have thus added a much-needed precision to diagnosis. Nevertheless, despite the ambitious claims sometimes made for their surgical treatment, it may not unjustly be said that intracranial tumours remain the forlorn hope of surgery, and, since the glioma and the secondary carcinoma together make up about half the total of intracranial tumours, they must of necessity remain so.

On the other hand the surgery of cranio-cerebral injuries is very inadequately represented in the literature of cranio-cerebral surgery, and this in spite of its manifestly greater importance than the surgery of tumours. Such injuries are extremely common and are on the increase. The author points out that in the United States there were 112,000 such cases in 1932. Further, as the author also rightly observes, their treatment is essentially a problem for the general surgeon. For these two reasons alone an authoritative and comprehensive account of their symptomatology and treatment is a crying need. Moreover, since the prognosis in adequately treated cranio-cerebral injuries is a vastly more hopeful affair than that of intracranial tumours, however skilfully these may be dealt with, the practical importance of a wide diffusion of knowledge concerning these injuries is clear.

This need the author has met in a wholly admirable manner in the book now under review. He has considered his problem as a whole, and from the points of view of everyone who may be called upon to deal with it, from the doctor who renders first aid at the scene of the injury to the surgeon who deals with the case in the "traumatic clinic." The requirements of treatment at each stage are fully described as also are the necessary diagnostic procedures.

The book is a complete manual of its subject and should be carefully studied by all who may be called upon to deal with head injuries. Its author has placed his professional colleagues under a heavy debt of gratitude to him for thus putting at their disposal so clearly and so judicially the fruits of his large experience.

JUNE, 1939

BRAIN.

PART 2, VOL. 62.

THE HISTOLOGY OF CEREBRAL ŒDEMA ASSOCIATED WITH INTRACRANIAL TUMOURS (WITH SPECIAL REFERENCE TO CHANGES IN THE NERVE FIBRES OF THE CENTRUM OVALE).

BY J. G. GREENFIELD.

(From the Pathological Laboratories, National Hospital, Queen Square.)

LOCAL œdema of the brain has long been recognized to occur round tumours and abscesses. More general swelling of the brain has been found also in cases of catatonia and epilepsy and has been thought to account for many of the symptoms of cerebral injury and uræmia. In spite of this there is much diversity of opinion as to the histological changes which accompany swelling of the brain and indeed, from what has been written, it would appear that different causes produce such different histological appearances that only confusion can result from any attempt to group them together.

General swelling of the brain has also been said to occur as an autolytic phenomenon so that if the post-mortem examination is delayed for more than twenty-four hours the convolutions may appear flattened and the sulci less patent than normal. Swelling of the brain tissue must also be clearly distinguished from the so-called œdema of the meninges which may be said to be the reverse of cerebral œdema since it results from shrinkage of the brain with the attendant widening of the subarachnoid space.

The normal correlation between brain volume and skull capacity was established by Rieger (1885), and Reichardt (1905), using his method, laid it down that the brain may be considered swollen when the difference between these measurements was less than 8 per cent. He initiated the conception of "brain swelling" which he defined as a definite increase in the volume of the brain, not due to hyperæmia or to excess of free fluid. This he found in katatonia, epilepsy, and various infections and intoxications. He considered it to be due to an alteration in the colloidal chemistry of the brain tissue which produced no definite histological changes. Wohlwill (1914) demonstrated the presence of Alzheimer's amœboid glial cells in many toxic and infectious diseases associated with brain swelling. Spatz (1929) distinguished "brain swelling" from œdema. In "brain swelling" there was a general increase in size of the whole hemisphere, with an increased consistency and a dry condition of the brain substance. In œdema the brain tissue was softer and wetter than normal. He described "symptomatic brain swelling" in cases of cerebral tumour which affected not only the whole of the hemisphere in which the tumour lay, but often also the opposite hemisphere. The medulla, as well as the uvula and tonsils of the cerebellum and the optic nerves, might be involved in the same process. He found little definite histological change in association with symptomatic brain swelling. In some cases there was swelling of the processes of the astrocytes in the white matter, often with dissolution of these processes (Clasmatodendrosis), and the amœboid change of Alzheimer which was more widespread than in any other condition. There were also slight swellings of the processes of the nerve cells in affected areas. Jaburek (1935), on the other hand, did not consider that any sharp distinction could be made in cases of cerebral tumour between brain swelling and œdema. He defined the histological changes of œdema as exudation of fluid with the formation of spaces and holes in the tissues, separation of the neuroglial meshwork, and of the perivascular and pericellular spaces. He found the greatest tendency to œdema in malignant tumours, such as carcinomas, fibro-sarcomas and many kinds of gliosarcomas, whereas the better differentiated gliomas, as well as the endotheliomas and angiomas, did not produce it. He considered that it was a toxic or inflammatory process spreading out from the tumour. He made the interesting discovery that certain tissues of the brain had a special tendency to œdema, whereas others were rarely affected. The white matter of the hemispheres was particularly liable, but the large commissural nerve tracts, such as the internal and external capsules, the corpus callosum and the anterior and posterior commissures were not affected. Other areas which were not affected were the grey matter of the cortex and basal ganglia, and the whole brain stem (including the cerebellum and the diencephalon). Scheinker (1938) also described œdema in cases of cerebral tumour. The histological changes found by him included increase of neuroglial nuclei, many of which were degenerated and their cell body disintegrating, congestion of vessels, widening of the perivascular spaces and general loosening of the ground substance, without any formation of neuroglial fibres or fat granule cells. He noted also irregular swelling of the myelin sheaths and axis cylinders and of the bodies of the neuroglial cells. In some places there were localized areas of softening of the tissues. In the cortex he found widening of the pericellular spaces, and acute cell disease of the neurones in the most affected areas. He also could find no sharp distinction between brain swelling and œdema; they were different grades in the same process of pathological hydration and swelling of the nervous parenchyma. While these authors laid special emphasis on the changes in the white matter, Le Beau (1938), on the basis of some experimental studies by del Rio Hortega, considered widespread swelling of the nerve cells of the cortex as the histological criterion of œdema in cases of cerebral tumour.

The histological changes in general swelling of the brain from other causes have been described by various authors. Struwe (1931) described the appearances in a number of cases of mental disease (catatonia, manic-depressive psychosis, epileptic dementia) in which death occurred suddenly from brain swelling. He found small localized areas in the white matter in which there was poverty or almost complete disappearance of myelin sheaths, those present being very thin or irregularly swollen. No products of lipoid katabolism were, however, seen. The axis cylinders in these areas were unaltered. Changes in the macroglia were more widespread and varied from clasmatodendrosis to complete destruction. The severest changes in it were seen in the cortex and the deeper layers of white matter, whereas it was relatively well preserved in the subcortical U fibres. In Sommer's sector of the Cornu Ammonis it was often completely destroyed. The Nissl picture of the cortex was, however, normal. Early progressive changes could be seen in the microglial cells and more pronounced changes in the oligodendroglia, the processes of which stained with unusual ease. In the cortex the oligodendroglial satellites might contain fine granules of iron. No vascular changes could be seen in these cases except congestion and occasional small hæmorrhages.

Terplan (1937) described the histological changes, associated with marked swelling of the brain, in two cases of insulin shock, three of acute encephalitis in children, one of which was associated with hypoglycæmia, one case of burns, one of poisoning by oleum chenopodium, and one of cerebellar cyst. In these cases there was swelling of the entire cortex with loss of its normal architecture. The nerve cells of the 3rd and 5th layers were almost entirely destroyed and those that remained showed colliquative or ischæmic necrosis. The endothelium of the capillaries was swollen. In one patient who lived for eleven days after the onset of unconsciousness the nerve cells of the 3rd layer of the cortex were replaced by a dense network of proliferating capillaries. These changes were not seen in the basal ganglia which were relatively normal.

It appears, therefore, that what is described as brain swelling in cases of insanity and various infections or intoxications may be a totally different histological process from the œdema related to brain tumours, on which, except for the assumptions of Le Beau, there seems to be a measure of agreement.

These histological studies have been supplemented by investigations of the relationship between the wet and dry weight of the brain tissues. Alexander and Looney (1938) found by this method that œdema was almost entirely confined to the white matter of the brain since the grey matter of œdematous brains kept the normal ratio between wet and dry weight. Both they and Schlüter and Never (1932) found, however, that it was impossible to judge the presence or the degree of œdema from a comparison of wet and dry weight since a relative increase of water was also found in atrophied and in hydrocephalic brains.

The difficulty of assessing the degree or even the presence of œdema in fixed brains makes it important to have some histological criteria. In cases of cerebral tumour the œdematous area is usually confined to the side of the tumour. As Jaburek has shown it does not affect the corpus callosum and is, therefore, unlikely to spread to the opposite hemisphere. It is, therefore, possible in these cases to compare the œdematous area with normal white matter from the same brain and thus avoid any fallacies arising from the mode of death or from post-mortem autolysis. It was also hoped that the study of the histology of œdema in relation to cerebral tumours might throw some light on its pathogenesis. It is recognized, however, that the process in cases of cerebral tumours may be quite different from that in general disease and intoxications, and no deductions as to the histology of general œdema or swelling of the brain should be drawn from the present study.

The macroscopic appearances of œdema in relation to cerebral tumours or abscesses are well known and in severe cases one can be certain of its presence. In such cases the white matter appears yellowish and soft, and when it lies on the slab fluid pours from it in considerable quantity. The degree of discolouration is variable and appears to depend to a considerable degree on the cause since it is usually greater in cases of cerebral abscess than in those of tumours. The discolouration gradually fades off as one passes away from the tumour or abscess to which the œdema is related, but it may be very extensive. In less severe cases there is no alteration in colour and the presence of œdema can only be judged from an increase in the size of the centrum semi-ovale and its softer consistence as compared with the normal hemisphere. In addition the convolutions look wider than normal from the swelling of their white centres. By comparison with the swollen white matter the cortex may look shrunken. Actually, by measurement it is found to be little, if at all affected. Œdema does not appear to occur either in the basal ganglia or brain stem. If it does it fails to cause any macroscopic changes. It may, however, affect the white matter of the cerebellum and is commonly seen round abscesses in that situation. Œdema of the spinal cord also occurs but is not considered in the present study which is confined to the cerebral hemispheres.

MATERIAL AND METHODS.

The material studied came from 28 cases of cerebral tumour. For purposes of comparison two cases of cerebral abscess were studied. Fairly large blocks of tissue, sometimes comprising the whole coronal section of a hemisphere were embedded in celloidin and stained by a variety of methods. For technical reasons frozen and paraffin sections were found less suitable than celloidin sections, but for certain methods frozen sections of material embedded in gelatine were used. Methods which depend on special fixation, such as Alzheimer's fuchsin-light green method, were not used. The latter method was used by Alzheimer and Wohlwill in extensive studies of the neuroglial reaction in cerebral œdema and other conditions, but for the purposes of the present study it was considered less important to study the neuroglial reaction intensively than to compare in neighbouring sections the changes seen in the astrocytes with those in the neurones including the axon and myelin sheath.

An earlier study of cases of old-standing injury of the brain had suggested that the widespread demyelination seen in these cases might result to some extent at least from cerebral œdema and, therefore, in the earlier cases of cerebral tumour examined only the Weigert-Pal method was used. This showed that characteristic changes in the myelin sheaths of the centrum semi-ovale of greater or less degree were constantly found in cases showing a degree of cerebral œdema which could be recognized by the naked eye. However, the fact that the changes to some extent resembled those produced by autolysis made it necessary to examine other elements such as the axis cylinders and neuroglia in which autolytic changes are more readily distinguished from those occurring before death. In addition to the ordinary tissue stains such as hæmatoxylin with van Gieson and Nissl's method, Mallory's phosphotungstic acid hæmatoxylin and in some cases Mallory's "connective tissue stain" (acid fuchsin-aniline blue-orange G.) were used for neuroglial cells and fibres, the Loyez method for myelin sheaths, and the Gros-Bielschowsky method for axis cylinders.[1] Lipoid degeneration was studied in sections from neighbouring blocks of tissue stained by Scharlach R and hæmatoxylin usually after gelatine embedding. The cases studied included five of metastatic malignant nodules in the brain, nine of endothelioma, one of hæmangioblastoma and thirteen of cerebral glioma.

ALTERATIONS IN NERVE FIBRES.

The most obvious change seen in cases of cerebral œdema studied by the Weigert-Pal method is a diffuse pallor of the centrum ovale. In most

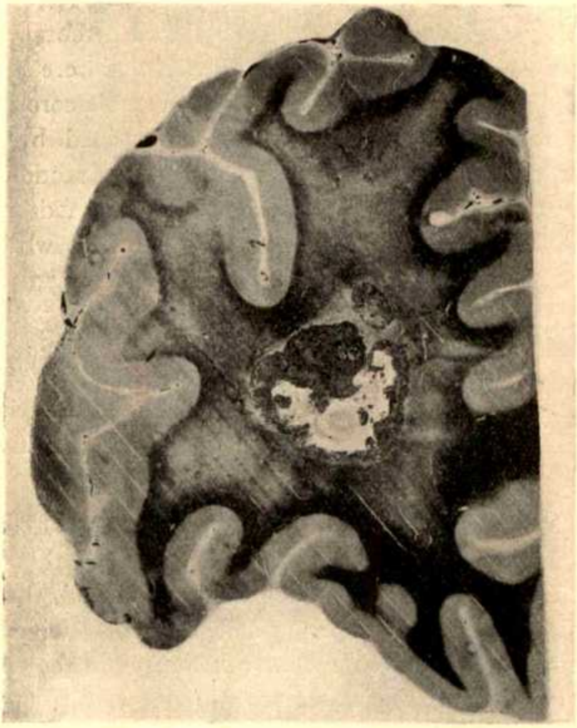

FIG. 1.—Secondary nodule from bronchial carcinoma embedded in white matter of frontal cortex. (Weigert-Pal counterstained with alum carmine.) There is a zone of œdema with partial demyelination round the nodule ; this spares the subcortical fibres in most places.

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[1] The Gros-Bielschowsky method employed was the modification for celloidin sections devised by Dr. D. Denny-Brown (Carleton, Histological Technique 2nd Ed.) to whom the writer wishes to express his gratitude for help in interpreting the changes in the axis cylinders.

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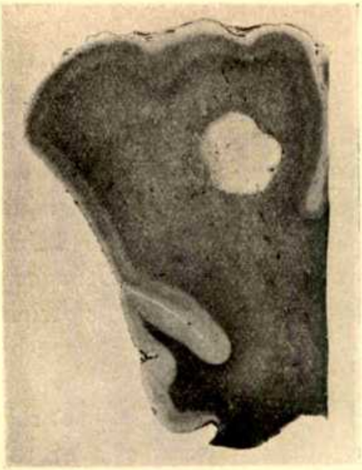

FIG. 2.

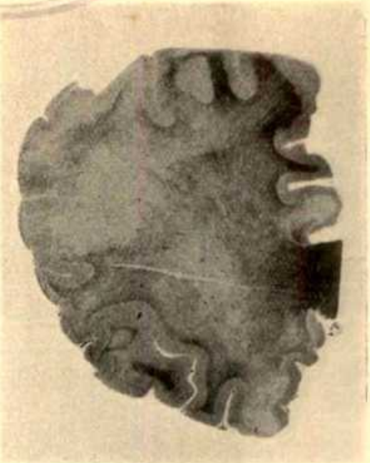

FIG. 3.

FIG. 2.—*Case 3.* Secondary nodule from renal carcinoma in subcortical white matter. The demyelination does not affect the myelinated fibres in the cortex (Loyez myelin stain).

FIG. 3.—*Case 3.* Coronal section through the frontal lobe and genu of the corpus callosum. There is widespread œdema and demyelination which, however, does not affect the corpus callosum. (Weigert-Pal.)

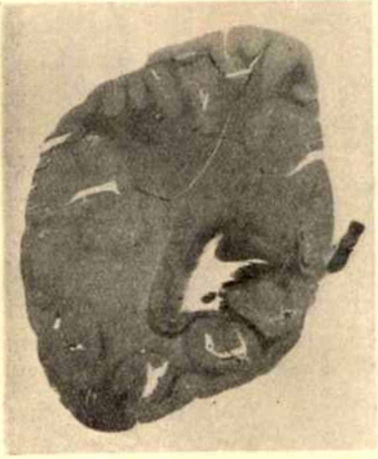

FIG. 4.

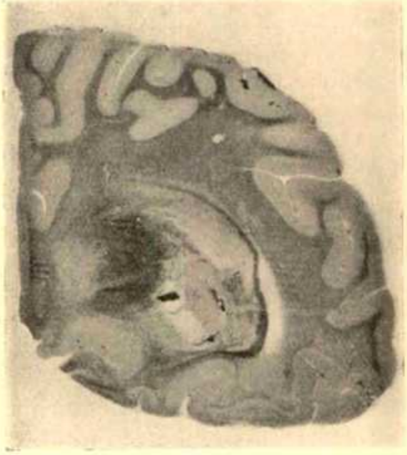

FIG. 5.

FIG. 4.—*Case 11.* Fronto-temporal glioma. Coronal section through right parieto-occipital region and splenium of corpus callosum. There is extensive œdema and demyelination which affects the optic radiations slightly and the corpus callosum not at all. (Weigert-Pal counterstained alum carmine.)

FIG. 5.—*Case 9.* Glioblastoma in relation to the posterior horn of the right lateral ventricle. Coronal section through right occipital lobe. The tumour (unstained) lies just internal to the ventricle. The optic radiations are stretched out by it but not demyelinated as much as the white matter external to them. The fibres going to the splenium of the corpus callosum, though they lie close to the tumour, are well stained. (Weigert-Pal counterstained carmine.)

cases this gradually recedes as one passes towards the cortex, but in severe cases it may be almost equally intense over the whole of the centrum semi-ovale, with the exception of the subcortical U fibres which are comparatively unaffected. In severe cases, and especially in those associated with cerebral abscess, these fibres also may remain comparatively unstained. There is a remarkable tendency for certain fibre systems to be spared either relatively or absolutely. For example the corpus callosum was never affected in the cases studied, and in cases involving the white matter of the occipital lobe the optic radiation was more deeply stained than the rest of the white matter (figs. 1-5). The possibility that pallor of the white matter might be entirely explained by a separation of the fibres by interstitial fluid is ruled out when the sections are examined under higher magnifications. It is then seen that very many of the fibres are beaded or irregularly swollen or show larger single swellings. These changes are as obvious in brains removed within an hour or two of death as in those in which a greater delay has occurred and are always more intense in the palely stained œdematous area than in those areas that stain more darkly. In severe cases the demyelination is much greater, and only sparse irregularly swollen myelin sheaths may be seen in the most affected areas, much of the lipoid appearing as fine granules or larger globules which stain with hæmatoxylin. But the margin is always indefinite, even when the transition from pale centrum semi-ovale to darker sub-cortical U fibres appears to the naked eye to be fairly abrupt (figs. 6-9).

In sections stained by Scharlach R it is unusual to find more than the earliest stages of myelin katabolism. A few phagocytic cells, especially near the vessels, contain granules which stain more orange than normal myelin, but very few granules which take the full red stain of fats or fatty acids can be seen. These early stages of myelin katabolism can be compared with the much greater degree of lipoid change which is sometimes seen in the softened zone immediately round the tumour. In the cases of cerebral abscess the katabolism of myelin had progressed much further, with the presence of many fat granule cells, but this was unusual in the œdema related to a cerebral tumour. Sometimes phagocytic cells (myeloclasts) could be seen inside the globular swellings of the myelin sheath, an appearance described by Jakob in secondary degenerations in the spinal cord (figs. 14 and 15).

The *changes in the axones* were studied in celloidin sections stained by the Gros-Bielschowsky method. They were less obvious than those in the myelin, and were in all cases of less severe degree, although in some severe cases, in which the œdema appeared to have been present for some days, considerable rarefaction of axis cylinders was found. In some cases in which the œdema appeared to be recent the axones were varicose, often with a ragged outline, and end bulbs were difficult to find, or were only seen on the fine fibres. In other severe cases end-bulbs and cocoon-like swellings on the course of the larger axones, and irregular swellings of the finer fibres, were seen in every microscopic field. In milder cases end-bulbs and large cocoon-like formations were absent or difficult to find, but many small fusiform swellings on the course of the fibres were seen. The latter appearance did not differ greatly from what may be seen in post-mortem autolysis, but it was as common in brains which were removed very shortly after death as in those in which there had been more delay (figs. 10, 11 and 12).

Neuroglial Reaction.

In all cases of moderate or severe œdema, swelling of the cell bodies of the astrocytes could be seen. This varied from the appearance of a small tag of cytoplasm at one side of the nucleus, to the presence of large bodied astrocytes, some of which had more than one nucleus. In certain cases there also appeared to be an increase in the number of astrocytes and it was not uncommon to find two or more lying close to one another as though they had arisen from the division of a parent cell. In bi-nucleated cells the nuclei might lie at opposite poles of the cell body, which was sometimes no wider than the length of the nuclei. Sometimes, however, they lay close together. Not uncommonly the nuclei in swollen astrocytes were irregularly enlarged, and might be elongated or reniform or even lobed like those of a polymorphonuclear leucocyte. In all except the most acute cases the enlarged astrocytes gave rise to fibres and in what appeared to be more chronic cases there was a definite or even great excess of neuroglial fibres throughout the œdematous area (figs. 18 and 21).

The appearance of the neuroglial cells in more acute cases were less easily analysed. Here the swollen cells were not all of one type as in the cases of less severity, but rather appeared to be divisible into four main groups. The first included cells with a large ill-defined irregularly shaped mass of cytoplasm, which appeared to fill up the interstices of the surrounding tissue rather than to push the fibres apart. It contained a nucleus which was sometimes of the size and shape of an astrocytic nucleus, but stained palely and diffusely (fig. 20). Sometimes these nuclei were so pale as to be invisible except with a high power objective. It was unusual to find reniform or elongated nuclei in this type of cell. Sometimes, however, the nucleus was shrunken and hyperchromic (pyknotic) but it never looked healthy.

The second type of cell, which might be seen in the same field as the first, but was much less abundant, consisted of a nucleus of normal astrocytic size but with scanty chromatin which was arranged as fine granules under the nuclear membrane, and a rather rounded cell body which was less swollen than in the first form, stained greyish with hæmatoxylin and sometimes appeared granular (fig. 16). A third type of cell had an irregularly shaped, sometimes swollen nucleus which often showed degenerative changes. The cytoplasm was swollen, irregularly rounded or oval and contained many fine granules (fig. 19). These three types were considered to be degenerating forms of astrocyte. None had any definite fibres attached to them, i.e. they had undergone clasmatodendrosis.

A fourth type of cell, which might be diffusely distributed, but was specially common near the walls of vessels, consisted of a small darkly staining nucleus which might be irregularly rounded, oval, reniform or elongated and a well-defined oval cell body full of fine granules, some of which stained purple with Mallory's phosphotungstic acid hæmatoxylin (fig. 17). This type of cell was thought to be derived from the microglia and to be an early form of lipoid phagocyte. The character of the nucleus and the tendency which these cells showed to collect near the walls of blood-vessels, suggested this derivation.

In cases in which these types of cell appeared there were often clear oval spaces in the tissues which usually did not contain any nucleus or cell. In only one case of cerebral tumour did they contain any stainable colloid and it appeared probable that they resulted from the shrinkage of the softened tissues during fixation and did not represent pre-existing spaces. It is important to note that in cases of this severity neuroglial fibres could not usually be demonstrated, though in one or two cases a few, rather thick, irregularly curved, neuroglial fibres could be seen, and occasionally smaller more granular fragments.

In each individual case the changes in the astrocytes tended to be of the same type and much the same degree, although their intensity decreased on passing toward the periphery of the affected area. They were found throughout the area in which the myelin stained palely but could no longer be found where the myelin was normal.

The *oligodendroglia* appeared to be little affected in the majority of cases studied. Only in acute and severe cases was there any evidence of swelling of the cell body and the changes then seen were scarcely more than those found in many cases in which the post-mortem examination has been delayed for twenty-four hours or more after death. The nuclei always remained relatively normal, although they sometimes appeared to be rather shrunken and their chomatin more granular than normal.

CEREBRAL CORTEX.

In the milder degrees of œdema related to tumours of the brain the cortex looked microscopically normal. There was no evidence of the generalized swelling of nerve cells which has been postulated by Le Beau as constituting the essential change of cerebral œdema. In only one case was there slight swelling of the neurones of the 5th layer, and this was interpreted as being an early axonal reaction due to the severe degeneration of their axones in the underlying white matter. In many of the severer cases ischæmic degeneration was seen in a certain number of the neurones. Its irregular incidence or patchy distribution indicated that it was not due to autolytic processes. It one case severer cell changes were present in some of the neurones of the 3rd layer. These cells were surrounded by fine granules due to degeneration and swelling of the boutons terminaux.

The slightness of the change in the cortex contrasted with those found in the cases of cerebral abscess and in one case of post-operative thrombosis of a superficial vein. In the former cases there was definite swelling of the bodies of the astrocytes and proliferation of the microglial cells as well as severe degeneration of many of the cortical neurones. These changes may be attributed to the direct effect of toxins emanating from the abscess. In the case of venous thrombosis most of the cortical neurones showed severe ischæmic changes; they were irregularly shrunken and many of them had receded from the surrounding tissues leaving a clear zone. In this case there was also some swelling of the cytoplasm of the astrocytes and increase in the numbers of microglial cells and oligodendroglial satellites. These changes resemble those seen in minor degrees of arterial obstruction and appear to result from anoxia of the tissues. Swelling of nerve cells was not seen either in this case or in others with extensive sinus thrombosis involving many of the large superficial cerebral veins.

Relations of type of tumour to severity and acuteness of the histological changes interpreted as "œdema."

It is generally recognized that severe œdema is more commonly associated with certain kinds of tumour than with others. Secondary carcinomas, for example, frequently appear to produce severe œdema round themselves, although at other times the masses of cancer are embedded in what appear to be healthy brain. It seemed, therefore, possible that an analysis of the relationship between the type of tumour and the degree or acuteness of the process, which it is convenient to call œdema, might throw some light on its pathogenesis. Although a much larger series of cases would be needed to establish this relationship in any definite manner, certain indications may be drawn from the comparatively small numbers in this series.

It will be convenient for the purposes of this analysis to assume that some idea of the duration of the œdema can be gained from the degree and type of reaction of the astrocytes. For example, it is generally agreed that the formation of new neuroglial fibres is a process requiring a certain amount of time. Whether this should be reckoned in hours or days is, however, a matter of speculation. The type of swelling of the cell bodies of the astrocytes which is associated with healthy nuclei and preservation of fibres also seems to be a change which requires some little time, probably several days, to develop. And, therefore, in cases in which the cell bodies were greatly swollen and in which many bi-nucleated cells were seen, the œdema was assumed to have existed for several days before death. On the other hand in cases in which the neuroglial swelling was of the amœboid type, with the presence of granular cells of microglial origin, it was difficult if not impossible to gauge the duration of the œdema, although its severity was evident enough. The changes in the axis cylinders are not much assistance in assessing the length of time that œdema has been present since these may be very precocious. Rand and Courville (1934) in cases of head injury found swellings and end bulbs on the small fibres as early as two hours, and larger end bulbs four hours after the accident.

Applying these criteria to the changes seen in this series of brains it was found that the most acute and severe changes, with the presence of amœboid glial cells, occurred in two cases of secondary carcinoma (one bronchial, the other renal), and three cases of glioblastoma, one of which had seeded over the walls of the posterior horns of the ventricles. At the other end of the scale mild diffuse changes, with the presence of Nissl's "plump" astrocytes and overgrowth of neuroglial fibres, were found in three cases of endothelioma and in four of the more slowly growing forms of glioma as well as in one case of secondary nodules from a hypernephroma. The other cases studied either showed early changes of moderate intensity or were complicated by some factor such as recent operation which made them unsuited for purposes of comparison. So far as one can draw any deduction from this survey it appears that rapidly growing tumours, whatever their nature may be, are apt to produce the more acute and severe degrees of œdema, whereas the slowly growing tumours usually give rise to a subacute process.

Nature and pathogenesis of œdema in relation to cerebral tumours.

The histological changes in the swollen areas of brain near brain tumours have been seen to include (1) Pallor of the myelin staining, due partly to separation of the fibres, and partly to changes in the myelin which may result in katabolism of much of it into granules and globules of material which still stains by hæmatoxylin. (2) Varicosities, irregular swellings, and the formation of end bulbs on the axones. (3) Swelling either of an acute and destructive (regressive) or a subacute and formative (progressive) character in the astrocytes. (4) Slight mobilization of the microglia with early lipoid phagocytosis.

Various questions as to the nature and pathogenesis of these changes arise. First, if not in importance at least in historical sequence, comes the old question whether the process should be called brain swelling or cerebral œdema. These terms have been applied to the macroscopical rather than the microscopical appearances: that of brain swelling to a condition in which the brain or a part of the brain is swollen, firmer than normal and dry, and œdema to a condition in which the brain is swollen, softer than normal and exudes fluid on standing. These criteria can only be applied to the brain in its fresh state, and it has been stated by Le Beau that areas which when fresh appear soft and wet may become, after fixation, firmer than the normal brain tissue. In the present series this was rarely found ; the areas which were soft when fresh never fixed firmly, and it was difficult, if not impossible, to obtain frozen sections from them without gelatine embedding. Pötzl and Schüller (1910), Jaburek (1936) and Scheinker (1938) in histological examinations of brain swelling and cerebral œdema found a gradual transition between the appearances in the two forms. This opinion is confirmed by the present study which indicates that the term œdema has been applied to the more acute and severe stages of a process which if less acute produces what has been called brain swelling.

It seems, therefore, best to use one name only for this process and the term œdema has been chosen. This name indicates that the swelling is due to fluid in the interstices of the tissue, but does not exclude the possibility of secondary changes in the cells and fibres. In the present series of cases it was found that myelinated fibres in œdematous areas were less closely packed together than in the normal brain, but histological evidence of interstitial fluid could only be found in one case. It appeared, therefore, probable that the substance between the fibres was not stainable by the methods employed. But that the fibres were separated by fluid there seems little doubt. The nature of this fluid cannot be determined by histological methods but it probably differs little from the normal interstitial fluid of brain tissue.

Of the histological changes which have been seen to occur in areas of œdema, the only one which is directly attributable to an increase of interstitial fluid is, therefore, the pallor in sections stained for myelin, due to separation of the fibres. The other changes are merely accompaniments of œdema and although constantly present in the present series, they may not always be associated with it. The question, therefore, arises whether they are independent or in some way dependent on the excess of interstitial fluid. That they are not related directly to the pressure exerted by the tumour is shown by the fact that they are rarely present in equal degree all round it; in fact the tissues may be normal histologically to within 1 cm. of the tumour on one side although the changes associated with œdema may spread for 5 cm. or more away from it in another direction.

The changes in the neuroglial cells and myelinated fibres are similar to those which are commonly found in cerebral anoxia, and anoxia in the neighbourhood of cerebral tumours might result either (1) from pressure on veins or involvement of veins in the tumour; (2) from capillary compression: or (3) from the stasis of interstitial fluid in the brain tissues. If the changes were due to anoxia their absence from tissues, such as the grey matter, which have a richer blood supply, could be readily explained.[1] Which of the three factors suggested is chiefly responsible for them in individual cases it is impossible to state on the evidence so far available. In cerebral tumours of all kinds there must come a time when the general intracranial pressure tends to compress the veins. This pressure is probably not evenly distributed within the cranial cavity owing to the firm dural septa and its greatest effects may be quite local. It was found, however, that dilatation of capillaries and small vessels was not a necessary accompaniment of œdema. It was found in this series only in the cases of endothelioma. If the abnormal transudation of fluid into the tissues were due primarily to this pressure on the veins, its anoxic effects would be increased by the compression of the capillaries, and a vicious circle would be established whereby the more the veins were compressed the more fluid would be transuded and the less room there would be for capillary blood. The simplest explanation for the association of the changes of anoxia with those of œdema is, however, the third suggested, i.e. that the stasis of excessive interstitial fluid in the issues prevents them from receiving their normal supply of oxygen from the capillaries.

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[1] On the other hand, it has been seen that ischaemic changes are often present in the cortical neurones.

The changes accompanying œdema in relation to cerebral tumours shed no light on its causation. The most probable causes are either pressure on veins, or the effects of toxins or metabolites from the injured brain tissue or from degeneration of the tumour itself. The possibility that tumours may involve more or less directly the veins which drain the œdematous area has already been mentioned. Metabolites from the damaged brain tissue or from degenerating tumour substance may cause œdema either by altering the osmotic relationship on the two sides of the vessel walls or by directly poisoning the walls of the capillaries. Of the latter process the histological studies in this series have given no evidence. While there may be severe destruction of myelinated fibres in the immediate neighbourhood of a tumour, the fact that the area of œdema is not necessarily concentric with the tumour is against the assumption that œdema is due to metabolites passing out from the tumour unless tissue fluids pass more freely in certain directions than in others. It can, however, be said that in some cases in which cancer nodules were embedded in the centre of the white matter of a hemisphere, the area of demyelination round them was almost concentric with the margin of the tumour.

ILLUSTRATIVE CASES.

Secondary Carcinoma.

Case 1.—C. R., aged 52. (Case No. 51/1937.) *Secondary nodules in brain from a bronchial carcinoma (Columnar celled carcinoma forming acini and alveoli).* Post-mortem examination twenty-four hours after death.

On removing the brain a superficial softened area in the right angular gyrus fell out, releasing rather thick mucopurulent material. In front and behind this area the right hemisphere was very soft and swollen. No other deposits of growth were found in the brain.

Histologically there was no increase of nuclei in the softened area of brain, and no evidence of inflammation except a single layer of lymphocytes in the perivascular space of one of the subcortical vessels. The cell bodies of all the astrocytes were swollen, some forming a rounded body about twice the diameter of the nucleus with sharply defined margins, others an irregularly defined mass of considerably larger size. In some of the latter the nucleus stained faintly and diffusely grey; in others the nucleus was considerably larger than normal and was paler and more vesicular than normal, its chromatin was arranged in coarse granules under the nuclear membrane and there was usually a well-stained nucleolus. Other smaller cells, in which the cytoplasm stained faintly grey with hæmatoxylin, had a pale nucleus of normal size in which the chromatin was present as fine granules. In addition rounded or oval granular bodies about 15 to 20 μ in diameter with a small rounded darkly-staining nucleus, placed eccentrically but not at the margin of the cell, were present in the most affected areas; some contained clear vacuoles and in occasional cells a single vacuole occupied most of the cell body, but more often several smaller vacuoles were present along with many fine granules. With Mallory's phosphotungstic acid hæmatoxylin a few fine, purple-stained granules were present in the swollen cells, both those with larger and smaller nuclei, but only a small proportion of the granules in the latter type of cell stained in this way. No neuroglial fibres could be seen in the softened areas. There was slight swelling of the cell bodies of the oligodendroglia throughout the section. This appeared to be no greater in the softened area than outside it.

In sections stained for myelin (Loyez method) there was diffuse pallor of the affected region, and under higher microscopic powers many irregular swellings and end bulbs were seen both on the coarser and finer fibres. In addition some irregular granular masses stained black by this method.

In sections stained for axones (Gros-Bielschowsky) all the fibres in affected areas were irregularly beaded with fusiform swellings (figs. 10 and 11), some of the larger fibres formed cocoon-like swellings or irregular varicosities on their course and a few definite end bulbs could be seen. The varicose beaded fibres in the affected area contrasted with the normal straight course of the fibres in unaffected parts of the same section. But in the cortex over the most softened area of white matter some of the fibres ran a wavy course or showed varicosities. Even this part of the cortex showed, however, much less involvement of the axones than the underlying white matter. The neurones in it showed no abnormality.

The changes in this case were considered to be severe and of comparatively short duration.

Case 2.—J B, aged 54. (Case No. 95/1938.)

Carcinoma nodule in the cortex of the right post-central gyrus about 4 cm. from the mesial margin of the hemisphere (secondary from an oat-celled carcinoma of the bronchus). Severe œdematous swelling of the white matter of the parietal lobe. Post-mortem examination 18 hours after death. In sections stained for myelin the pale zone spread up to the cortex in the most affected areas, but the subcortical U fibres and the line of Baillarger in the cortex were well stained.

Histologically the tissues looked almost areolar, from the separation of the ground substance, and contained many large-bodied cells. Most of these were swollen astrocytes, usually with one, but occasionally with two, nuclei of normal appearance (fig. 19) In addition there was a considerable sprinkling of smaller more rounded cells, with a granular cytoplasm and small darkly-stained nucleus In some of these the cytoplasm stained grey with hæmatoxylin.

In sections stained by phosphotungstic acid hæmatoxylin there were numerous fibres throughout the swollen area many of which could be traced to the large-bodied astrocytes. Many of the granules in the small granular cells stained purple, but no such granules could be seen in the astrocytes. Loyez myelin method showed irregular varicosities and swellings on the fibres in the œdematous area with many larger fusiform swellings and end globules, as well as granular masses which stained black. The myelin in the overlying cortex looked relatively healthy. In Gros-Bielschowsky sections many fusiform or cocoon-like swellings were seen on the fibres and there were many large end bulbs; a few showed varicosity or feathery irregularity of outline, but the majority appeared to be only slightly affected In the overlying cortex most of the axones had a normal contour, but some had irregular thickenings on their course. In the cortex over the swollen area there was a tendency for the neurones, neuroglial nuclei and vessels to separate from the matrix, usually on one side only, an appearance which suggested undue shrinkage. A few of the nerve cells showed slight ischæmic change, but the majority were healthy.

The changes in this case were considered to be of moderate severity and of fairly long standing.

Case 3.—C. K., aged 71. (Case No. 109/1938.)

Carcinoma of the kidney removed five years earlier with secondary deposits in the brain and cerebellum. No operation. Post-mortem examination 12 hours after death. No evidence of excessive intra-cranial pressure. The cerebral tumour was embedded in the inferior surface of the right frontal lobe attached to the dura mater. Swelling of the brain extended from this to the outer surface. In Weigert-Pal sections the white matter of the frontal lobe was very extensively affected, but the corpus callosum stained normally black (fig. 3). On the outer surface of the frontal lobe the subcortical fibres were not preserved. The layer of myelinated fibres in the cortex could still be seen however (fig. 2).

In all sections the tissues had a loosely reticular appearance in the regions affected owing to the presence of large oval spaces which contained a clear colloid matter staining faintly by van Gieson's counter stain. From the large size of the spaces and the absence of nuclei from almost all it appeared that they represented serous exudate into the tissues. The nerve fibres were separated rather than destroyed by them. In addition there were very numerous, more definitely cellular, large bodies, only a few of which had a definite outline. Most of these contained a degenerated nucleus which either stained diffusely and palely or had fine granules of chromatin under the nuclear membrane. Other astrocytes were only slightly swollen; their outline was fairly sharp and more rounded than normal and the chromatin of their nuclei was usually unduly granular. No typical "plump" cells were seen.

In sections stained by phosphotungstic acid hæmatoxylin no neuroglial fibres could be seen in the swollen area, and only a few of the swollen cells contained purple granules. Loyez method showed very great irregularity of contour of almost all the myelin sheaths in the affected area, with many large globules, and a smaller number of small black-staining granules which lay singly in the tissues. The large oval spaces contained no stainable lipoid. In Gros-Bielschowsky sections the larger axones were swollen rather irregularly and a few end bulbs or large fusiform swellings were seen on them. The finer fibres showed many small fusiform swellings, varicosities and end bulbs. In the cortex overlying the swollen area the large pyramidal cells of the 5th layer showed early chromatolysis (axonal reaction) and a few of the smaller neurones had the shrunken cytoplasm and darkly-stained nucleus of ischæmic degeneration. Cells of this kind were scattered irregularly among normal neurones, but in one small area almost every neurone was affected in this manner.

The changes in this case were interpreted as being acute and recent.

Case 4.—E. S., aged 62. (Case No. 35/1937.)

Secondary deposits from a Grawitz tumour of the kidney which had been removed six years earlier. Post mortem 15 hours after death. No evidence of intracranial pressure. The tumours lay in the cortex of the right parietal and occipito-temporal regions, the larger nodule being near the anterior end of the calcarine fissure. Diffuse œdema extended out from the latter tumour to the external surface of the occipital lobe. The subcortical U fibres were affected in some places under the outer cortex. In the immediate neighbourhood of the tumour there was some vacuolation of the tissues but no stainable substance could be seen in the oval clear areas. Throughout the swollen area all the bodies of the astrocytes were swollen, and some had two nuclei. In some places they seemed to be more numerous than normal. No other change was visible in these areas in sections stained by hæmatoxylin and van Gieson. A diffuse increase in the number of neuroglial fibres could be found throughout the swollen area in sections stained by phosphotungstic acid hæmatoxylin. Loyez method showed separation and beading of the myelin sheaths, but the changes seen were comparatively slight. By the Gros-Bielschowsky method fusiform swellings were seen on a large proportion of the fibres and a few large end bulbs were seen. The changes in this case were interpreted as being subacute.

Case 5.—F. H. (female), aged 60. (Case No. 74/1936.)

Left vertico-frontal endothelioma. Post-mortem examination forty-eight hours after death, which was directly due to pontine hæmorrhage. There was considerable herniation of the hippocampal gyrus through the incisura tentorii, and considerable swelling of the left frontal lobe. In sections stained for myelin there was diffuse pallor of the swollen area running out to the cortex in some places, but in others stopping short at the arcuate fibres.

Histological examination.—This showed distension of all the vessels which were otherwise normal. The cell bodies of all the astrocytes were irregularly swollen to a varying degree. Their outlines were irregular and their nuclei often elongated or irregularly lobed, and many of the nuclei stained palely and diffusely. Occasional bi-nucleated astrocytes were present. A few rounded clear globules which stained a bright orange with van Gieson's counterstain were seen In the most affected area a narrow zone of pink staining cytoplasm was seen round the oligodendrocytes which otherwise appeared unaffected. Throughout the swollen area there was a diffuse excess of neuroglial fibres which was no longer seen on passing to unaffected areas. Loyez stain showed many large globules of swollen myelin and irregularity of contour of most of the fibres. By the Gros-Bielschowsky method a few end bulbs were seen. There was also some varicosity and irregular thickening of both the fine and coarse fibres, but the changes found by this method were relatively slight. The cortex appeared normal.

The case was interpreted as showing an acute change superposed on a more chronic œdema.

Case 6—J. S., aged 19. (Case No. 103/1936.)

A large endothelioma had been removed from the right frontal lobe on the day before death. It had involved the precentral convolution. Post-mortem examination thirty-six hours after death There was considerable erosion of the base and the inner table of the vault of the skull by pressure. There was diffuse swelling of the white matter behind the cavity from which the tumour had been removed. In sections stained with iron hæmatoxylin and van Gieson, the majority of the astrocytes were seen to have greatly swollen irregularly-rounded cell bodies and a marginal nucleus which either stained normally or was paler and more granular than normal. Some of the astrocytes appeared as a smaller, rounded, rather granular mass of cytoplasm which stained faintly with hæmatoxylin, and had a centrally placed nucleus in which the chromatin was arranged in fine subcapsular granules. Many of the microglial cells had globular, rounded cell bodies with no visible granular inclusions. The oligodendroglia appeared normal. No excess of fibres was seen in sections stained with phosphotungstic acid hæmatoxylin. In Gros-Bielschowsky sections there was an unusual number of cocoon-like and fusiform swellings on the larger axones (fig. 12). The finer fibres showed many varicosities and fusiform swellings. Loyez method showed many larger and smaller swellings on the myelinated fibres and considerable separation of the fibres with many oval lacunæ between them, some of which were filled with the cell bodies of swollen astrocytes.

Many of the changes seen in this case appeared to be of too long standing to have dated from the operation, but some of the more acute changes were no doubt due to this.

Case 7.—F. B., aged 47. (Case No. 105/1938.)

A large left frontal endothelioma had been removed by operation twenty hours before death. At the post-mortem examination it was found that the posterior anastomotic vein, which connected anteriorly with a vein which had been clipped just behind the operation wound in the cortex, had become thrombosed throughout its course. There was, however, no thrombosis of the left lateral sinus. There was considerable œdema of the white matter behind the area occupied by the tumour.

Histologically, in areas near the tumour cell, stains showed moderate swelling of the bodies of all the astrocytes and oval clear areas between the fibres. There was also a considerable overgrowth of neuroglial fibres. By Loyez method there was diffuse pallor of the white matter which diminished on approaching the cortex. The myelinated fibres in the affected area showed very numerous swellings on the course and at the end of fibres. By the Gros-Bielschowsky method an unusual number of end bulbs and fusiform swellings on the course of the fibres was seen.

In the parietal lobe in the territory drained by the thrombosed vein, the appearances were similar. The temporal lobe under the thrombosed vein was much less affected, and apart from a slight degree of ischæmic change in the cortical neurones showed little abnormality. It seemed likely, therefore, that the changes seen near the tumour were associated with pre-existing œdema, and were not related to the venous thrombosis.

Case 8.—G. C., aged 49. (Case No. 81/1938.) *Glioma Cerebri.*

Glioblastoma near the vertex of the left parietal lobe. Post-mortem examination twelve hours after death. Small cerebellar and uncinate pressure cones were present on the left side. The right cerebellar hemisphere was much smaller than the left; this appeared to be a developmental abnormality. There was considerable swelling below and in front of the tumour. In sections stained by Loyez method this area appeared diffusely pale, but the subcortical U fibres were spared in most places.

Histologically, in sections stained by hæmatoxylin and van Gieson, very few normal astrocytic nuclei could be seen. A few cells with a comparatively small well-defined cell body which stained grey with hæmatoxylin had a nucleus of astrocyte size, in which fine granules of chromatin lay under the nuclear membrane (fig. 16). Many large, irregular, ill-defined clear masses of cytoplasm were seen with a degenerated nucleus which stained very palely and diffusely so that they were scarcely recognisable under low powers (fig. 20). These were considered to be degenerated astrocytes. There was also a smaller number of cells with a rather large lobed degenerated nucleus and a granular cell body which probably represented another form of degeneration of astrocytes. The oligodendroglial nuclei were normal. Many were surrounded by a small, clear zone of cytoplasm. Here and there inside a large myelin swelling could be seen a microglial phagocyte with a relatively large granular cell body and very shrunken nucleus (myeloclast) (figs. 14 and 15).

In sections stained by phosphotungstic acid hæmatoxylin a few wavy irregular neuroglial fibres remained, but the greater number appeared to have broken up and granular chains or short lengths of degenerated fibres could be seen irregularly scattered through the tissues or collected in phagocytic cells. By Loyez method the fibres were extremely irregular in outline with innumerable swellings on their course and terminations and there was also a large number of small collections of black granules of lipoid. The Gros-Bielschowsky method showed a great number of swellings and end bulbs, as well as irregularity of contour of the fibres. By contrast the fibres in the cortex overlying the most affected area of white matter were relatively healthy, although a large proportion of the neurones here, especially those in the deeper layers, showed severe ischæmic changes.

In sections stained by Scharlach R various stages of myelin katabolism could be traced up to the formation of small, rather brightly-staining orange granules, but no red globules or granules could be seen. The widespread degeneration of astrocytes and the severe changes in the axones and myelin in this case indicated its acute nature.

Case 9.—E E., aged 34. (Case No. 34/1936.)

Glioblastoma of right occipital lobe below and internal to the posterior horn of the ventricle. No operation. Post-mortem examination eighteen hours after death.

The white matter of the right occipital lobe was diffusely swollen and in Weigert-Pal sections stained palely with the exception of the optic radiations and some of the subcortical fibres which stained relatively dark. A wide zone of fibres belonging to the forceps major (i.e. going to the splenium of the corpus callosum), although lying close to the inner margin of the tumour, stained relatively darkly (fig. 5).

In hæmatoxylin van Gieson sections the bodies of the astrocytes were all irregularly but not greatly swollen , many of their nuclei were swollen and pale, with finely granular chromatin ; some were lobed or reniform, others were rather shrunken and stained more deeply than normal But a large proportion preserved their normal appearance. The oligodendroglial nuclei were normal, but a narrow crescent of cytoplasm could be seen on one side of most of them. In the overlying cortex a large proportion of the neurones showed ischæmic change, and some of those in the third layer were shrunken and degenerated and were surrounded by granules representing swollen boutons terminaux (incrustation of Golgi network) (fig. 13). No neuroglial fibres could be seen in the swollen areas of white matter.

In sections stained by the Gros-Bielschowsky method there was great irregularity in the outline of the axones and many swellings on their course. In Weigert-Pal sections all the fibres showed large swellings on their course, and a few small collections of free granules of lipoid were also present. The changes in this case appeared to be recent and of a subacute nature.

Case 10.—F. H., aged 56. (Case No. 6/1939.)

A firm glioma was present in the left supramarginal and angular gyri with a cyst in its inferior part. It was adherent to the overlying dura mater. No operation had been performed. The post-mortem examination was made less than twelve hours after death. The white matter internal to the tumour was swollen and in Weigert-Pal sections stained palely. This pale area was limited below by the fissure of Sylvius and internally by the posterior limb of the internal capsule.

In hæmatoxylin van Gieson sections the astrocytes in the swollen area had irregularly swollen cell bodies, sometimes of large size. Their nuclei showed slight degenerative changes ; many stained diffusely and palely, in others the chromatin was broken into fine granules. In most of the cells with the latter type of nucleus the cell body was comparatively small and of a greyish colour. A few microglial phagocytes with rather large oval or rounded granular body were seen near the walls of the vessels. A few of the neurones in the overlying cortex showed a slight degree of ischæmic change. None were swollen. The neuroglial fibres were increased in number. The majority preserved their normal outline but a certain number showed granular disintegration, varicosity and other evidence of degeneration.

In Gros-Bielschowsky sections many of the axones were irregularly thickened, others showed fusiform swellings, and end bulbs were very numerous.

In Weigert-Pal sections many irregularly thickened sheaths were found with lateral spicules or globules, and all the thicker sheaths had large fusiform swellings on their course. Most of the finer fibres had broken down into a detritus of fine lipoid granules.

By Loyez method the alterations in the myelin seemed rather less acute, but an enormous number of fusiform and irregular swellings was seen as well as many black-staining free granules. This section passed through a less severely affected area than that used for the Weigert-Pal method.

There seemed to be an old standing gliosis in this case with more acute changes superimposed.

Case 11.—A. L., aged 40. (Case No 8/1939.)

A rounded mass of glioma spanned the anterior part of the right Sylvian fissure invading the upper surface of the temporal pole and the overlying frontal lobe. No operation was performed. The post-mortem examination was made fourteen hours after death. There was diffuse swelling of the right hemisphere behind the tumour extending backwards beyond the splenium of the corpus callosum. At this level Weigert-Pal sections showed diffuse pallor of the white matter with relative sparing of the optic radiations. The splenium of the corpus callosum was of the normal black colour.

In sections stained with hæmatoxylin and van Gieson all the astrocytes were swollen with normal nuclei and an asteroid cell body giving rise to fine processes. Bi-nucleated astrocytes were not seen. No other abnormality was seen either in the white matter or the overlying cortex. There was a considerable excess of neuroglial fibres in the affected area of white matter.

In Weigert-Pal sections the myelin sheaths showed a certain amount of beading, but this was slight by comparison with that seen in most of the cases. The changes in the axones in Gros-Bielschowsky sections were also slight although fusiform swellings and end bulbs were fairly numerous.

This case showed only slight, and apparently early, changes.

Case 12.—J. H., aged 45 (Case No. 11/1939.)

A cellular localized astrocytoma composed of pyriform and fusiform cells was present in the upper part of the left parietal lobe. A craniotomy had been performed less than twenty-four hours before death. At the post-mortem examination which was made thirty-six hours after death a well-marked uncinate pressure cone on the left side with bruising of the right crus was found. There was a moderate degree of swelling of the white matter of the parietal lobe under the tumour and this in Weigert-Pal preparations showed as a diffuse pallor of staining with preservation of the subcortical U fibres and the corpus callosum.

In sections stained with hæmatoxylin and van Gieson the bodies of all the astrocytes were moderately swollen : their nuclei were normal or slightly enlarged ; a few were elongated or uniform An occasional cell had two nuclei A narrow crescent of cytoplasm could be seen round many oligodendroglial nuclei. The neurones in the overlying cortex were healthy. There was an excess of neuroglial fibres amounting to a fibrous gliosis throughout the affected area (fig. 21); this disappeared as the subcortical zone was reached.

In Weigert-Pal preparations the number of myelinated fibres seemed greatly reduced, and those that were present had many large swellings on their course. In Gros-Bielschowsky sections also there was a poverty of axones and those that were present showed considerable irregularity of contour. Large cocoon-like swellings on the thicker axones were very abundant in this case.

The changes in this case were considered to be of considerable duration Although only slight changes were demonstrated by nuclear and cell stains, they were associated with severe degeneration of the nerve fibres and with great neuroglial sclerosis.

SUMMARY.

A histological study was made of 28 cases of cerebral œdema related to cerebral tumours. In these cases œdema was found to be constantly associated with definite histological changes of the following kinds:—

(1) The myelin in the centrum ovale stained palely, but that in the large commissural tracts, such as the corpus callosum, the internal capsule and the optic radiations, was relatively or absolutely normal. The pallor of staining was due partly to separation of myelinated fibres, but also to degeneration of the myelin, which in severe cases might be broken up into granules and globules.

(2) The axones were less affected than the myelin, but showed degenerative changes such as beading, irregularity of contour, end bulbs and cocoon-like swellings on their course. The axones in the cortex were relatively or absolutely normal.

(3) The astrocytes in the white matter were always swollen. In the less acute cases they appeared as Nissl's "plump" astrocytes and there was an excess of neuroglial fibres. In more acute cases the astrocytes showed clasmatodendrosis and various degenerative changes in the nuclei.

(4) The microglial cells in the affected areas were mobilized in the

early stages of phagocytosis of lipoid. The oligodendroglial cells were relatively normal.

(5) Vascular congestion was only found in cases of endothelioma. There was no evidence of endothelial proliferation or of distension of the Virchow Robin spaces. In most cases the vessels appeared to be unaffected.

(6) The neurones in the overlying cortex might show some ischæmic degeneration in severe cases. Both the myelin and axones were relatively unaffected in the cortex and subcortical zone.

These changes were considered to be due to anoxia of the tissue of which the chief cause was probably the excess of interstitial fluid, but venous obstruction and reduction of the size of the capillary bed may have also played some part in its production.

The most severe and acute changes were found in cases of rapidly growing tumours (secondary cancers and glioblastomas). Changes of a more subacute type might occur in association with tumours of slow growth (endotheliomas and astrocytomas).

In these cases no sharp distinction can be made between "brain swelling" and cerebral œdema; what has been described as œdema is a more severe degree of the same process as "brain swelling." The general "brain swelling" which occurs in general infections and intoxications may be associated with quite different histological changes from those found in association with cerebral tumours.

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LEGENDS FOR PLATES.

PLATE III.

FIG. 6.—*Case 9* Right occipital glioblastoma. The myelin sheaths in the most œdematous area are very scanty and those present show many bulbous swellings on their course or at their terminations. (Weigert-Pal counterstained alum carmine.)

FIGS. 7 & 9—*Same case as fig. 1.* Secondary nodule from bronchial carcinoma There is extreme loss of myelin sheaths in the œdematous area behind the tumour. Much of the myelin has broken up into fine granules of lipoid. The sheaths that remain are irregularly beaded with larger and smaller swellings. (Weigert-Pal counterstained carmine.)

FIG. 8.—*Case 3.* Secondary nodules in right frontal lobe from a renal carcinoma. The myelin sheaths are irregularly swollen and many granules of lipoid lie free in the tissues. (Weigert-Pal counterstained alum carmine.)

PLATE IV

FIG. 10—*Case 1.* Secondary nodule from bronchial carcinoma. Numerous end bulbs are seen on the finer fibres. (Gros-Bielschowsky.)

FIG 11.—*Case 1.* Large skein-like end swellings are seen as well as swellings and end-bulbs on the fine fibres. (Gros-Bielschowsky.)

FIG. 12.—*Case 6.* Right frontal endothelioma removed on day before death. Cocoon-like swelling on a fibre in the œdematous area behind the tumour (Gros-Bielschowsky.)

FIG. 13.—*Case 9.* Right occipital glioblastoma. Neurones from third layer of cortex on the outer surface of the occipital lobe. The central neurone shows severe ischæmic change, with staining of the swollen *boutons terminaux* round it. (Hæmatoxylin van Gieson.)

PLATE V.

FIGS. 14 & 15.—*Case 8* Glioblastoma of left parietal lobe. Myeloclasts are seen inside swollen myelin sheaths. (Iron hæmatoxylin van Gieson.)

FIG. 16.—*Case 8.* A slightly swollen astrocyte with a pale nucleus containing fine subcapsular granules. (Iron hæmatoxylin van Gieson.)

FIG. 17.—*Case 8.* Microglial phagocyte containing fine granules of lipoid lying beside a capillary. (Iron hæmatoxylin van Gieson.)

FIG. 18.—*Case 5.* Fronto-vertical endothelioma. A swollen bi-nucleated astrocyte is seen with much overgrowth of neuroglial fibres. (Mallory's phosphotungstic acid hæmatoxylin.)

FIG. 19.—*Case 2.* Secondary nodule from a bronchial carcinoma. Two swollen astrocytes are seen one of which has a multi-lobular nucleus. (Iron hæmatoxylin van Gieson.)

FIG. 20.—*Case 8.* Four swollen astrocytes with pale diffusely-stained nuclei are seen among the darkly-stained oligodendroglial nuclei. (Iron hæmatoxylin van Gieson.)

FIG. 21.—*Case 12.* Astrocytoma of left parietal lobe. Diffuse gliosis in the œdematous area remote from the tumour. (Mallory's phosphotungstic acid hæmatoxylin.)

PLATE III.

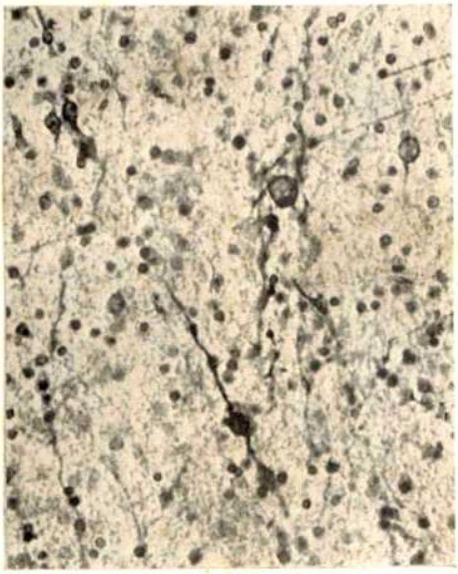

FIG. 6.

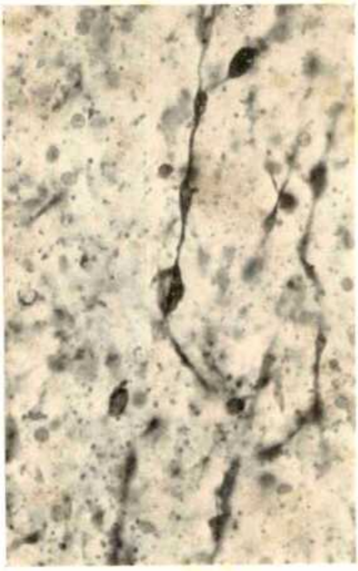

FIG. 7.

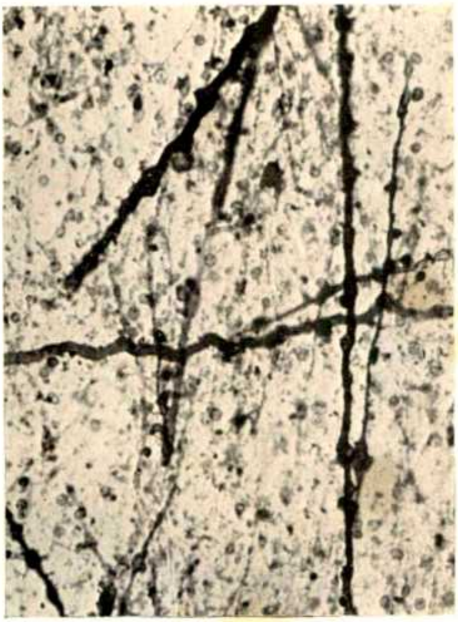

FIG. 8.

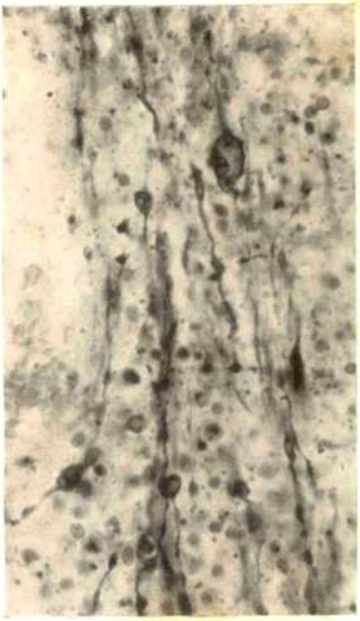

FIG. 9.

To illustrate article by J. G. Greenfield.

PLATE IV.

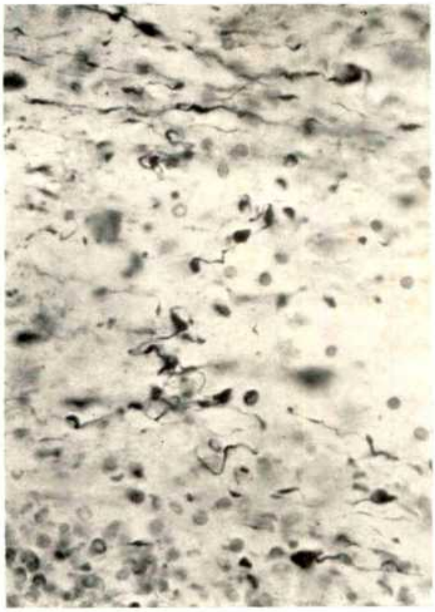

FIG. 10.

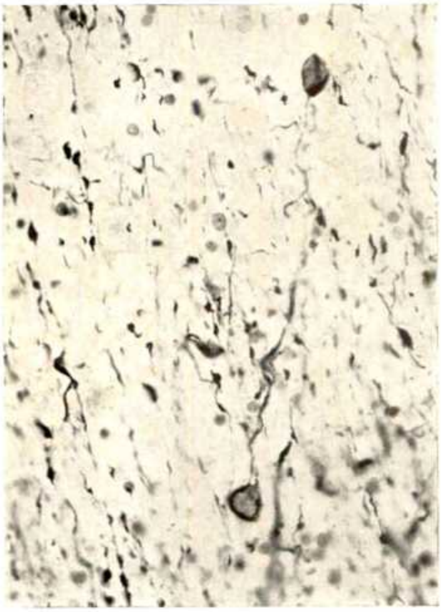

FIG. 11.

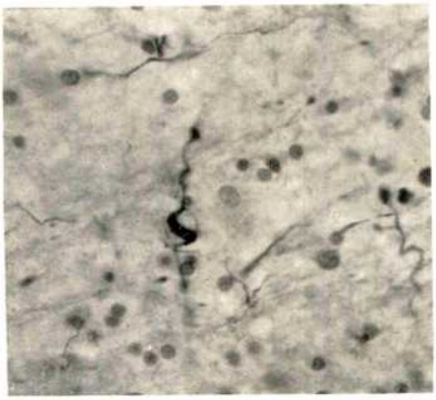

FIG. 12.

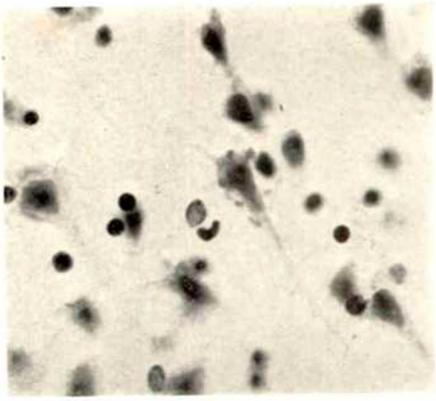

FIG. 13.

To illustrate article by J. G. Greenfield.

PLATE V.

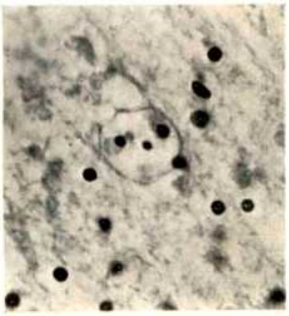

FIG. 14.

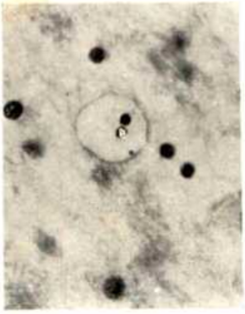

FIG. 15.

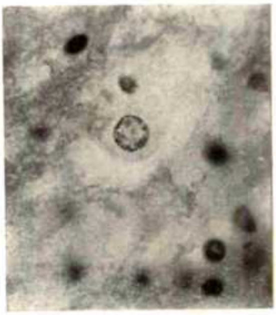

FIG. 16.

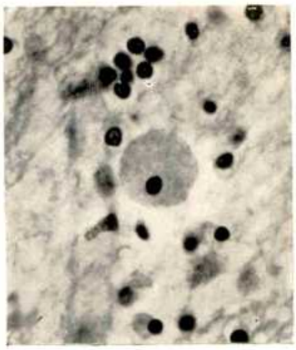

FIG. 17.

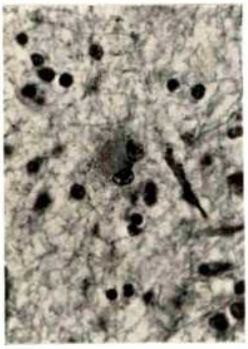

FIG. 18.

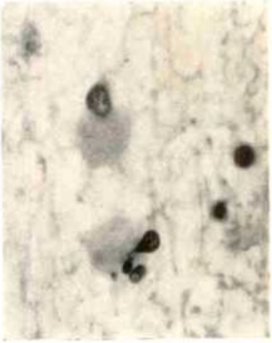

FIG. 19.

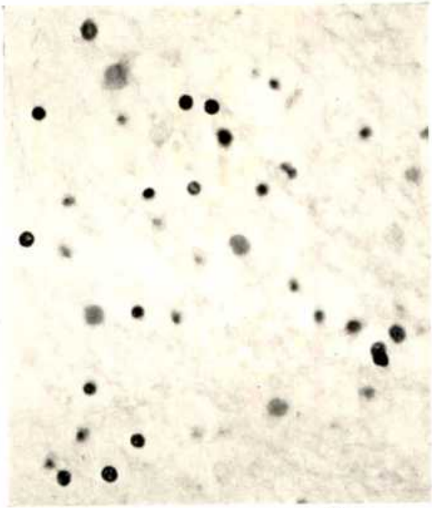

FIG. 20.

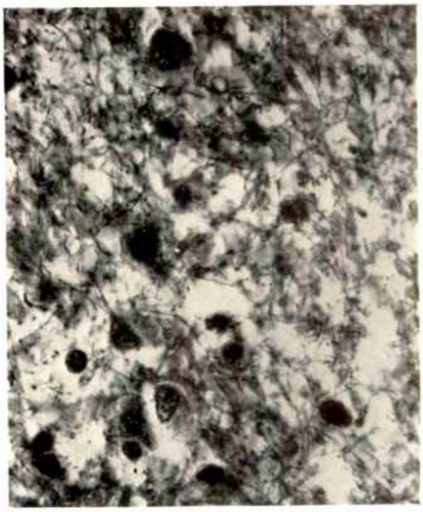

FIG. 21.

To illustrate article by J. G. Greenfield.

THE POTASSIUM CONTENT OF MUSCLE IN DISEASE.

BY J. N. CUMINGS.

(From the Biochemical Laboratory, National Hospital, Queen Square, London.)

THE potassium content of human voluntary muscle has received very little attention; more especially is this so in disease processes affecting muscles. Leulier, Pommé and Delaye (1931) and Leulier and Pommé (1932) showed that in a few common nervous and muscle disorders, such as progressive muscular atrophy, there was a normal potassium content of the affected muscles.

The present paper records the potassium content found in muscles in a variety of diseases, with special reference to dystrophia myotonica and myasthenia gravis, in which conditions no previous investigations of a similar nature appear to have been made. The effect of the administration of prostigmin upon the muscle potassium has also been studied.

METHODS AND MATERIAL.

Muscle was obtained in almost every case by biopsy from an affected area and the potassium content estimated as previously described (Cumings, 1939). The effect of prostigmin upon the muscle potassium was determined in some cases of myotonia and myasthenia gravis. In such patients, after muscle had been removed, prostigmin (mgm. 1) was administered subcutaneously, and after half-an-hour another piece of muscle removed. The serum potassium in one case of myasthenia gravis was also examined before removal of any muscle and again after the second piece had been taken.

RESULTS.

The cases in which normal potassium contents in affected muscles were found are given in Table I.

Abnormal muscles containing a low potassium concentration are seen in Table II. This group consists of muscles containing a large excess of fat (pseudo-hypertrophic muscular dystrophy) or of fibrous tissue (peroneal atrophy) and of muscles from patients with myotonia.

Lastly, in Table III are shown the results from five patients with myasthenia gravis in whose muscles there was a raised potassium content.

TABLE I.

Name	Disease	Potassium in grm. % of wet weight	Potassium in grm % of dry weight
C.	Progressive muscular atrophy ...	0·34	1·18
G.	" " " ...	0·23	0·93
P.	Simple atrophy	0·287	0·966
K.	Charcot-Marie-Tooth	0·21	0·954
D. K.	Myositis	0·263	1·13
Gr.	Wasting associated with cerebral tumour	0·22	0·99
L.	Peripheral neuritis, right side ...	0·27	1·15
	" " left side ...	0·288	1·49

TABLE II.

Name	Disease	Potassium in grm. % of wet weight	Potassium in grm. % of dry weight
W.	Pseudo-hypertrophic muscular dystrophy	0·102	0·204
M.	Peroneal atrophy, right side ...	0·132	0·402
	" " left side ...	0·085	0·229
L.	Marked atrophy with fibrous tissue replacement	0·23	0·55
F. S.	Myopathy with marked fibrosis ...	0·195	0·369
V.	Myotonia	0·14	0·532
B.	"	0·302	0·454
S.	"	0·19	0·74

TABLE III.

Name	Disease	Potassium in grm. % of wet weight	Potassium in grm. % of dry weight
Mrs. W.	Myasthenia gravis	0·376	1·522
Mr. B	" "	0·697	2·61
Mrs. B.	" "	0·568	2·28
Miss H.	" "	0·49	2·33
Mr. D.	" "	0·364	1·504

Results of Prostigmin Administration.

Muscles from two normal subjects, two cases of myotonia and two cases of myasthenia gravis were investigated. The results are shown in Table IV. The potassium content in dry muscle only is given in order to show the results more clearly, but the findings were comparable in both dry and wet weight of muscle.

TABLE IV.

Name	Disease	Potassium in grm. % of dry weight	
		Before prostigmin	After prostigmin
L.	Normal	1·23	1·49
I.	"	1·12	1·12
B.	Myotonia	0·454	0·606
S.	"	0·74	1·47
H.	Myasthenia gravis	2·33	1·0
D.	" "	1·504	0·613

DISCUSSION.

It has been shown that normal muscle contains a potassium content that may vary from 0·2 to 0·35 grm. per cent. of wet weight and 0·8 to 1·2 grm. per cent. of dry weight (Cumings (1939)) and it is seen that in all except a very few diseases there is a normal muscle potassium content. Muscles with gross replacement by fibrous tissue or fat show a marked diminution in potassium content and this is to be expected, as Gersh (1938) has shown that the potassium is contained in the muscle fibre and that there is practically none in the interstitial tissue.

The most marked exception to normal potassium content occurred in muscles from myotonia and myasthenia. In myotonia there was a very marked diminution in potassium content and this cannot be accounted for by the lack of muscle fibres, for although this did exist, the potassium was estimated in relation to weight of muscle examined. Also macroscopic and microscopic examination showed practically no increase in fibrous tissue. There has also been shown to be a diminution in muscle potassium content in experimental nutritional muscular dystrophy in animals (Fenn and Goettsch, 1937).

The very marked increase in potassium content in muscles from cases of myasthenia may be of considerable importance.

The effect of prostigmin on muscle potassium was interesting. Muscles from normal patients showed no appreciable alteration in potassium content after the administration of prostigmin. Muscles from cases of myotonia and of myasthenia showed after prostigmin an approach to the normal muscle potassium level. Concurrently with the return to a normal potassium level there was a return to normal muscle function in patients with myasthenia gravis. Patients with myotonia showed no clinical improvement, either as regards the myotonia or their normal muscle function, although the potassium content approached the normal, and this was not surprising, as all the muscles showed some signs of atrophy.

One case of myasthenia (Table IV, D) showed a rise in serum potassium after prostigmin. The resting level was 25·2 mgm. per cent. and this rose to 36·47 mgm. per cent., so that it appeared that the potassium liberated from the muscle passed into the blood.

The method of action of prostigmin upon the muscle potassium and the fate of the liberated potassium are now being investigated.

SUMMARY.

The potassium content in muscles in various nervous and muscle disorders has been estimated, especially in muscles in myotonia, in which there is a low potassium level, and in myasthenia, in which a high potassium level is recorded.

Prostigmin has been shown to produce a rise in the potassium level in muscles from cases of myotonia, and a fall in potassium in myasthenic muscles.

It is with pleasure that I thank the Staff of the National Hospital, Queen Square, for allowing me to utilize material from patients under their care.

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SEVERE DEMENTIA ASSOCIATED WITH BILATERAL SYMMETRICAL DEGENERATION OF THE THALAMUS.[1]

BY K. STERN.

(From the National Hospital, Queen Square, London.)

THE following is the report of a case for which no analogy could be found in the literature. Apart from this interest, which is offered from the point of view of mere peculiarity, it appears to throw more light on the question of disturbance of thalamic functions, and to contribute to the morbid anatomy of the thalamus.

CLINICAL HISTORY.

The patient, a man of 41 years, was admitted to the National Hospital under Dr. F. M. R. Walshe on February 9, 1938.

The patient's history was obtained from his wife. His father and mother were alive and well. One brother and one sister were alive and well; none had died There was no history of nervous or other disease in the family. The patient's wife was well.

Previous to the present illness he had always been healthy, active and energetic. His wife knew of no previous illnesses, accidents or operations. During the war he was in Mesopotamia and India for four years; he was in hospital once while serving abroad, but the nature of this illness was not known.

Until May, 1937, nine months before his admission to the hospital, he was always active, healthy, and alert, working in a chemist's shop. In May he gradually became "run down," complained of pain in his left shoulder and "was felt to be in need of a rest." In July he was becoming more inert, was always licking his lips and complaining of his mouth being dry. He developed marked thirst and polyuria, which persisted for two months. He also became very drowsy. He fell asleep after every meal, slept heavily at night, and was difficult to wake in the morning.

In August, 1937, he had to give up work, and subsequently he gradually lost his speech. He used to be a good talker, but in the last six months before admission he had steadily become more silent and his voice had become weaker. He did not use wrong words, nor was there any apparent difficulty in expression; it was simply that he spoke less and less. His understanding was impaired: "when asked to pass one thing he passed something else." He became unable to write and could scarcely read, though he looked at the picture papers.

He grew slowly and steadily worse, becoming very slow in all his movements and completely inert. There was no obvious depression, no tremor or paralysis of the limbs. His mind wandered and he often made remarks with no bearing on the conversation. He talked nonsense and described himself as doing things which he was known not to have done. His memory was very poor, and he did not seem to know that he was ill. He appeared to think he was still at work, and in bed performed the actions appropriate to his work, for example, the dispensing of a prescription.

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[1] This work was carried out while holding the Kathleen Schlesinger Research Fellowship.

He had no headache or vomiting, neither "fits" nor attacks of unconsciousness. Squint, diplopia, or loss of vision were never observed. When he was admitted to hospital he had no polyuria, he had never shown any sign of incontinence. He was able to walk about two miles, but he was very slow and rather unsteady. His legs tired easily and he shuffled; there was, however, no dragging of one leg or any marked deviation, and he had not fallen. His general health was good. He ate well, chewed and swallowed normally. He had lost a little weight. Digestion was normal. Cough or dyspnœa were never observed.

On examination he presented the picture of a fairly-healthy-looking, well-built man. His speech and articulation were normal, apart from the content of the former. He had a worried, rather sullen and stuporose expression. He was extremely restless and constantly shifted about in bed, rearranging the sheets, making as if to get up, rubbing his head and face. There were numerous mannerisms, such as pointing in a grotesque way, sucking his lips, and a striking tendency to repeat actions and words once elicited. After the tongue had been put out, its protrusion was for some time the invariable response to any other command. He ignored the attempt at examination and repeatedly buttoned up his pyjamas or turned on his side—not, however, in the manner of an active resistance, but as if he did not recognize what was wanted. There was no obvious lack of comprehension, but he was extremely uncommunicative and frequently ignored any question or command. There was a striking tendency to repeat the question, or to answer by a simple rearrangement of the questioner's words. The whole mental atmosphere was weird, uncanny and crafty.

Specimens of Conversation.

What is your name?	(Answered correctly.)
How old are you?	"Eighteen." (Ten minutes later said "eight or nine.")
Where are you?	"Just thinking where I'd like to be."
How long have you been here?	"Four or six months."
Where were you before?	"The room very similar to the other one, but perhaps a different build."
What is the date?	"Jan. 25 or 26, I think."
What year?	"203." (Persists in 203 to repeated questioning.)
Who is the King?	"King George."
What number?	"209."
When did the War begin?	"209."
How long did it last?	"209."
When did it finish?	"About 209—I can't think about that like I do about other things."
What do you think of?	"Scent of spray."
What are you interested in?	"Everything."
What are you most interested in?	"Most things."
What most of all?	"Right things most."

Cranial nerves.—The optic discs were of normal colour and the edges were sharp. The vessels and the retinæ were normal. The pupils were of moderate size, equal, central and circular. They were fixed to light and also on convergence, which was very poor. The external ocular movements were full in all directions, without strabismus or nystagmus. There was no ptosis, enophthalmos or exophthalmos. The jaw opened and closed normally. The corneal reflexes were brisk and equal. There was a slight left lower facial weakness at rest or on movement. There was no tremor of the mouth or eyelids. The palate rose in the mid-line. The tongue was protruded in the mid-line; there was no tremor, wasting or fibrillation.

Upper limbs.—The power was good and equal in all muscle groups. There was neither rigidity nor tremor, wasting nor fibrillation. There was no gross ataxia, but he introduced perverse movements into co-ordination tests.

Lower limbs.—There was no wasting or weakness. Frequent movements and rigidity of a voluntary order made the examination difficult. It could, however, be stated with certainty that there was no ataxia

Sensation could not be tested.

Reflexes.—All tendon-jerks were symmetrical and very brisk, especially in the upper limbs. The abdominal reflexes were sluggish and equal. The plantar responses were indefinite owing to voluntary posturing and withdrawal.

The heart and chest were normal on examination.

Lumbar puncture.—The pressure was 160 mm., and the final pressure 140 mm. The fluid was clear and colourless. No cells were seen. The amount of protein was 0·020 per cent. Nonne-Apelt and Pandy reactions were negative. Lange's test did not show any change. The Wassermann reaction was negative in the cerebrospinal fluid and in the blood.

A radiogram of the skull did not reveal any sign of intracranial growth.

On February 22, 1938, a bilateral ventricular puncture was performed. The cortex seemed further away from the dura than in normal cases. Both ventricles were entered without difficulty at an equal and normal depth. The ventricular pressure was not raised. The ventricular fluid did not show any abnormalities on routine chemical and microscopical examinations

On numerous occasions during the period between his admission to hospital and his death, the patient showed the following phenomena.

Sucking: with eyes open.—If the examiner's finger, or a pencil, were brought close to either angle of the mouth, the moment this object came into the patient's view a pursing movement of the lips was made on the side from which the object approached The protruded lips parted and the object was seized between them and sucking movements followed. This was as readily elicitable from one angle of the mouth as the other, and could be repeated many times in quick succession.

With eyes closed.—The lip protrusion and sucking occurred at once if the stimulating object made contact with one corner of the mouth.

Grasping.—Grasping movements, of some force and marked rapidity, were elicitable from either hand.

With eyes open.—If the examiner's finger—within the patient's view—were approached to the gap between the thumb and index finger of the patient's hand, a grasping movement at once was made. On contact these digits closed round the examiner's finger. Contact of the examiner's finger with the palm of the patient's hand led to quick closure of the latter.

With eyes closed.—Contact alone—as described above—elicited these movements.

Tonic grasping.—Any attempt to withdraw the examiner's finger from the patient's grasp—unless so carefully and slowly attempted as to avoid all movement of, or fresh contacts with, the patient's hand, evoked strong tonic grasping. The effective stimulus appeared to be stretching of the finger flexors.

During this period the patient was fatuous and incapable of sustained attention. The sucking and the grasping movements appeared to be carried out automatically and without special attention on the patient's part once the appropriate stimulus was provided. Even when he lay drowsy and with eyes closed sucking and grasping movements were elicitable once the necessary contact with the stimulating object was made.

These phenomena persisted until the final state of coma.

SUMMARY OF CLINICAL HISTORY.

A man of 40 developed rather rapidly the picture of a severe organic dementia with drowsiness. The dementia was a general one with gross lack of memory and orientation, a tendency to perseveration, combined with considerable changes of personality, such as inertia and a complete lack of initiative. From the statement that he spoke of " doing things which he was known not to have done " it appeared that the gaps of memory were filled by confabulations, a phenomenon familiar in Korsakoff's syndrome. One the other hand, focal symptoms such as aphasia apraxia, and agnosia, appeared to be absent. The only neurological signs were the loss of the pupillary reflex to both light and convergence, the sucking reflex, and the grasping phenomena.

In view of the rapid mental deterioration with signs of severe cortical impairment combined with loss of the pupillary reflex, although not of a true Argyll-Robertson character, the diagnosis of general paresis seemed obvious. This, however, could not be confirmed by serological examination. There were no clinical signs of arteriosclerosis or of arterial hypertension ; thus a diffuse vascular disturbance could also be excluded.

The remaining possibilities were an intracranial neoplasm, or some rarer condition such as presenile dementia (Alzheimer's disease) or circumscribed cortical atrophy (Pick's disease). These two last-named diseases have never been observed accompanied by disturbance of the pupils, whereas it is known that ocular signs may occur in supratentorial tumours (Collier, 1904). Therefore the picture of severe mental deterioration accompanied by very marked grasping phenomena, and yet unaccompanied by signs of raised intracranial pressure, led finally, by the exclusion of all the other possibilities, to the diagnosis of a neoplasm of one or both frontal lobes. The bilateral ventricular puncture, however, did not add anything to confirm this diagnosis. Thus, when the patient lapsed into the final stages of coma, the diagnosis had not been sufficiently clear to justify an exploratory craniotomy.

Post-mortem.—The body of a rather thin middle-aged man with recent parietal burr holes for ventriculography. Brain and spinal cord only removed. No thickening of skull ; dura quite lax. No herniation. Meninges and vessels normal No evidence of cerebral atrophy. Brain weight (unfixed) 1,270 grammes.

Microscopical examination.—Blocks from the cerebral hemispheres, from the cortex, basal ganglia, lower brain-stem, medulla oblongata, and the cerebellum, and spinal cord were examined in frozen and in celloidin sections. The methods of Weigert-Pal, Nissl, Bielschowsky, v. Braunmühl, Bielschowsky-Gros, Herxheimer (scharlach R), Wilbur Smith (myelin sheaths), Holzer, Mallory (phosphotungstic acid hæmatoxylin), and Van Gieson were applied Brodmann's areas 1, 3, 4, 6, 8, 9, 10, 11, 17, 18, 19, 23, 24, large blocks from the temporal, parieto-occipital and occipital regions, and blocks from the hippocampal region of both hemispheres were examined partly with Nissl's method and partly with myelin-sheath preparations on ordinary celloidin (Smith and Quigley, 1937). The right thalamus was cut completely in serial coronal sections (15 μ), and each fifth section stained with thionin. Of the left thalamus, parts had already been used for Weigert-Pal and frozen sections in routine examinations, therefore only two large horizontal blocks of the left basal ganglia could still be used for serial sections (15 μ), every fifth section being stained with thionin.

The meninges were normal everywhere, except for a perivascular collection of round cells in the temporal region. The vessels were normal everywhere. In the left putamen some of the perivascular spaces were enlarged and contained a few fat granule cells, the vessels themselves being perfectly normal.

The cortex showed diffuse pathological changes which were accentuated in certain areas and less distinct in others. They were nowhere focal or sharply circumscribed and so could not be detected with the lowest powers. These changes were not very characteristic ; there was a certain degree of lipoid atrophy of ganglion cells with a considerable amount of glial overgrowth in which all kinds of glia cells took part. This change was most marked in the lower and middle layers of the cortex. The arrangement of glia cells was loose and irregular, the single elements being rather swollen ; thus the gliosis appeared to be rather recent. The degree of these changes varied from a slight gliosis, such as could be encountered in any brain after intercurrent internal disease, to a conspicuous degree of cell proliferation. The cyto-architecture of the cortex, however, was nowhere disturbed. The areas mainly affected were the posterior parietal region and the temporal region, and small parts of the granular frontal cortex, on the whole more on the right than on the left side. The greater part of the granular frontal cortex, however, was free. The posterior limbic region (area 23) was affected on the left side.

Fat staining (scharlach R) showed a considerable amount of lipoid degeneration of ganglion cells. Numerous capillaries all over the examined parts of the cortex showed fat granule cells and fat-containing endothelial cells.

The white matter presented the picture of an even, dense, cellular gliosis. Here, too, some capillaries showed fat granule cells. In one area near the posterior part of the corpus callosum there was a large perivascular collection of fat granule cells. In myelin preparations (Weigert-Pal, Wilbur Smith) the subcortical white matter and the centrum semiovale were normal. The axis cylinders (Bielschowsky-Gros) appeared normal. In glia fibre preparations (Holzer) there were numerous large fibrous astrocytes distributed all over the white matter and over the inferior layers of the cortex. There were also monster glia cells. Those cells were arranged loosely

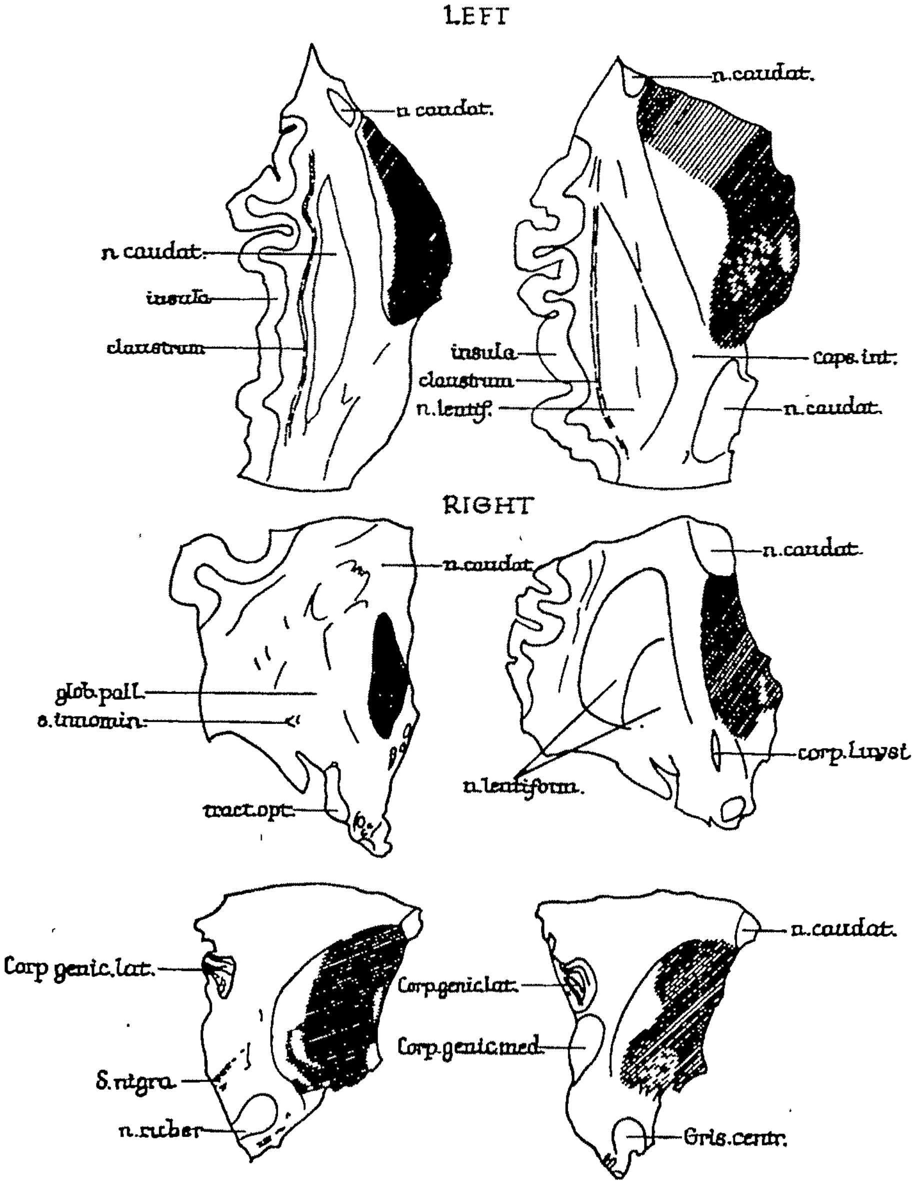

FIG. 2.—Representative sections from basal ganglia of both sides in camera lucida drawings. The left basal ganglia were cut in horizontal sections (upper 2 pictures). The degenerated areas are shaded.

or in small foci, and there was no dense fibre network as one might expect from the degree of cellular gliosis.

Basal ganglia.—The most striking pathological finding in this case presented itself in the thalamus on both sides. There were areas which were completely devoid of ganglion cells (fig. 1), and others in which a comparatively few sclerotic ganglion cells were scattered within a dense and even gliosis. The preserved areas in the right thalamus were as follows—(fig. 2) the ventral and arcuate nucleus (mainly ventricular nucleus b and c of Monakow), (fig. 3) cells of the zona reticulata, most of the irregularly scattered medial "hyperchromatic" nuclei (n reuniens of Malone, mid-line nuclei of Le Gros Clark), (fig. 4) including the massa intermedia, and both the lateral and medial geniculate bodies. The anterior nucleus, the medial nuclei in the proper sense, the centro-median nucleus, and the lateral nuclei had disappeared. The habenular ganglion was preserved. On the left side, as far as could be seen from the remaining blocks, the picture was the same. Here, in an area corresponding to one of the medial nuclei, a considerable collection of fat granule cells and macrophages was found. The medullary laminæ, especially the external one, showed a marked gliosis which made them stand out on naked-eye inspection. In Bielschowsky-Gros preparation a regular network of axones was still preserved in areas which were devoid of all ganglion cells (fig. 5). Preparations with phosphotungstic acid hæmatoxylin (Mallory) demonstrated the dense and even distribution of fibrous astrocytes and monster glia cells over the whole of the degenerated area. In marked contrast to this picture silver stains of the mesodermal elements (Klarfeld-Achuccaro) did not reveal any form of reaction. The borderline between diseased and preserved parts in the thalamus was sharply defined.

Apart from a considerable amount of lipoid pigment in ganglion cells, the remaining parts of the basal ganglia (corpus striatum, globus pallidus, corpus subthalamicum) and the preserved areas of the thalamus were normal. The hypothalamic nuclei, the mid-brain, and the examined parts of the lower brain-stem were normal, except for a certain amount of gliosis with neuronophagia in the superior colliculi and a complete atrophy of considerable sectors of the inferior olive on both sides. This atrophy was somewhat symmetrical and affected the medial parts of both the ventral and dorsal bands.

Trial sections from various areas of the cerebellum (Nissl, Bielschowsky-Gros. Van Gieson) and from various levels of the spinal cord (Nissl, Weigert-Pal) were normal. The pituitary gland was normal.

Discussion of Pathology.

Reviewing the histopathology of this case one can state that all the findings, the main lesion in the thalamus, and the less conspicuous findings in the cerebral cortex and inferior olives, have one essential point in common—viz. parenchymatous degeneration with consequent glial reaction. An inflammatory condition may be excluded from the findings both in the meninges and in the central organ, quite apart from the clinical picture.

There are various possibilities as to the nature and origin of these parenchymatous lesions. At first sight one might be inclined to think of a vascular basis for the entire process. The extra- and intracerebral vessels, however, were normal, and the clinical picture itself makes it unlikely that the case was one of arterial hypertension with histologically normal arteries. It is true that the slight diffuse gliosis in the cortex and the sector atrophy of the inferior olives, both of which were accompanied by a corresponding gliosis, belong to the type of lesions encountered in diffuse vascular disease such as arteriosclerosis. A closer study of the thalamic lesions, however, is against the assumption of an ischæmic lesion. The fact that in the areas of complete disappearance of ganglion cells a network of fine axis cylinders obviously of afferent neurons was preserved, excludes this possibility. A degree of ischæmia sufficient to destroy all the nerve cells of an area and to provoke a vast glial overgrowth, and yet on the other hand not sufficient to destroy axis cylinders in the same area, is inconceivable. Moreover, an ischæmia of such a degree would in every case be followed by a glial *and* mesodermal reaction; the complete absence of capillary proliferation is therefore to be regarded as further evidence against an ischæmic lesion. Apart from these features, which exclude with certainty a vascular origin of the lesion, there are others which would make it extremely unlikely even if nothing else were known. Firstly, the site of the lesion does not coincide with any known area of vascular supply; e.g. the same arterioles which supply the medial thalamic nuclei ("artères thalamo-perforées," Foix and Hillemand, 1925) supply also the zona incerta and the anterior part of the red nucleus both of which were intact in the present case. Secondly, the border of the lesion coincides exactly with the border of the thalamus towards the internal capsule and the caudate (fig. 1). Another feature, quite uncommon in vascular diseases of the basal ganglia, is the fact that the lenticular nucleus and the internal capsule are intact, and that the process is confined to the thalamus in an apparently symmetrical manner.

Having thus excluded inflammatory and vascular processes the range of possibilities is considerably lessened. The main question that remains is whether the degeneration is a retrograde one, such as is observed after damage to the thalamo-cortical neuron by a cortical or subcortical lesion. The histological picture, viz. the simple disappearance of ganglion cells and purely glial overgrowth, and the preservation of such functional units as the ventral thalamic nucleus and the geniculate bodies, makes this suggestion a likely possibility.

Before going into this question any further it is necessary to discuss the pathological changes in the cortex and white matter observed in this case. The clinical picture was one of severe subacute presenile dementia;

syphilis could be excluded, and the possibilities of a frontal lobe tumour, a circumscribed cortical atrophy (Pick) or a diffuse presenile degeneration (Alzheimer) remained. Pick's disease is characterized by an atrophy of certain parts of the cortex, most frequently in the frontal or temporal lobe, which is visible to the naked eye, and which produces a considerable diminution of the weight of the entire organ. Even in cases at an initial stage of the disease the circumscribed atrophy is macroscopically visible, at least after ablation of the meninges (v. Braunmuhl, 1930). Histologically the atrophy always begins in the upper three layers of the affected cortex. Thus it is quite obvious that the present case has nothing in common with the well-defined anatomical picture of Pick's disease.

As to the question of "premature ageing," one cannot deny that the diffuse pathological changes of the cortex and white matter, viz. lipoid degeneration, cortical and subcortical gliosis, and the atrophy of the inferior olives, are such as might be found in any senile brain. On the other hand, all localized parenchymatous system atrophies occurring in adult life, such as certain cerebellar atrophies and Huntington's chorea, are usually accompanied by the same kind of diffuse cortical and subcortical changes. This fact is important when we consider the pathology of the present case, because the cortical and subcortical changes, even in the areas of most marked degree, are certainly not sufficient to explain the thalamic degeneration as a retrograde one. In adult or senile brains much more severe atrophy of the cortex or gliosis of the white matter may occur without considerable thalamic changes. Even in Pick's circumscribed cortical atrophy any minor changes in the basal ganglia, which may be found, are, strangely enough, confined to the extrapyramidal system. Only in one case (Grünthal, 1936) were thalamic changes found, but these were apparently confined to postero-medial areas, and, judging from the photomicrograph, appear as marked subependymal gliosis rather than as true degeneration.

The somewhat symmetrical atrophy of the inferior olives belongs apparently to the same category of lesions as the diffuse subcortical and cortical changes. von Braunmühl (1928) has demonstrated how often, for some unknown reason, such bilateral "sector" atrophies occur in any sort of cerebral disease. The integrity of the cerebellum in the present case excludes the possibility of a retrograde degeneration. The so-called "thalamo-olivary tract," the origin of which in the thalamus is still doubtful, was preserved at the level of the medulla. Therefore the atrophy of the inferior olives cannot be due to transneuronal degeneration.

From these facts it appears, by the exclusion of all other possibilities, that this is a genuine case of a system degeneration in the thalamus. There is, moreover, positive evidence for this assumption as there are here features typical of all parenchymatous system degenerations, e.g. those of the cerebellum or the lenticular nucleus. These features are: (1) the apparent symmetry of the process; (2) the "simple atrophy," i.e. the fact that the fatty products of degeneration are remarkably scarce compared with the extension and degree of degeneration; (3) the fact that the unaffected parts represent a developmental entity. The last-mentioned point is of the greatest theoretical interest and therefore needs special attention. Huber and Crosby (1929) have shown that the ventral nucleus and the geniculate bodies originate from a common matrix which is phylogenetically the oldest thalamic structure. The mid-line nuclei are very largely developed in lower mammals, and become inconspicuous in primates. These are just the formations which are bilaterally preserved in the present case. According to Edinger's well-known theory, in all the system degenerations which are due to what he called "abiotrophy," the process affects the more recent structures first or exclusively. This theory has been applied, sometimes with insufficient evidence, to the pathology of cerebellar atrophies, of Pick's disease (Onari and Spatz, 1926), of Huntington's chorea, and of various other conditions. Edinger's theory is particularly significant in the present case. Although care is necessary in making deductions from a single case unsupported as yet by analogies in the literature, the phylogenetic facts mentioned above bring more evidence for the assumption that here we have a genuine system degeneration.

There is some pathological evidence that other degenerations of this type, particularly the genuine cerebellar atrophies, be brought on by extraneous causes, such as chronic alcoholism (Jakob, 1912), malignant tumours (Greenfield, 1934), intestinal intoxication (Rossi, 1907), and may be associated with system degenerations. As it was impossible to carry out a complete post-mortem examination in the present case this question must be left open. However, the frequency of such toxic conditions and the great rarity of the associated degenerations in the central nervous system indicate that there must be, in certain individuals, a pre-existent constitutional factor—an "endogenous" vulnerability of the affected systems (Scherer, 1933).

It is not possible to bring the present case into relation with any previously defined pathological picture. The widespread disease of the basal ganglia and cortex first described by Jakob (1921) and usually quoted in the literature as "Jakob-Creutzfeld's disease" leads to considerable areas of gliosis in the thalamus, mainly its medial nuclei. There, however, the thalamic changes are only part of a picture which is essentially that of a motor disease. This can best be understood from the term by which Jakob first described the condition, i.e. "spastic pseudosclerosis." It is characterized by a combined disease of the extrapyramidal and pyramidal system and the lower motor neuron. The degeneration of the cortex in area 6, of the striatum, and of the globus pallidus, are always most marked. All these features were completely absent in the present case, and, on the contrary, one of its most striking features was the contrast between the degenerated thalamus and the intact lenticular nucleus.

From this it is obvious that the present case cannot possibly be classified even as an "atypical" form of Jakob-Creutzfeld's or any other known disease. It is best described without attempt at classification as a case of bilateral symmetrical degeneration of the thalamus, excluding the ventral nuclei and geniculate bodies, and possibly including the "pretectal" area, rostral to the mid-brain. The last-mentioned area is not sufficiently defined in man; therefore it is possible that along with the medio-caudal periventricular parts, structures were involved which do not belong to the thalamus proper.

CLINICO-ANATOMICAL ASPECT.

The most striking symptom in this case was the severe dementia which dominated the entire clinical picture. Common neurological experience shows that one has to be very careful in correlating disturbances of such complex functions as intelligence, attention and initiative, with lesions of any particular structure in the brain. It was, however, pointed out above that the fresh gliosis of the cortex and of the white matter are not sufficient to explain the mental disturbance; on the other hand, the destruction of large thalamic areas on both sides was so complete that one cannot avoid correlating this lesion with the clinical picture. Moreover, in contrast to neoplastic and inflammatory lesions, any general damage to the entire organ, e.g. from the mechanical or circulatory disturbance, can here be excluded with certainty. This makes the present case particularly valuable from the point of view of localization.

A previous investigation (Smyth and Stern, 1938) made it appear probable that the severe mental deterioration occurring in certain gliomas of the thalamus is related to the function of that structure, and has not only the significance of a general symptom of intracranial growth. Even gliomas which neither cause hydrocephalus nor invade adjoining structures to any considerable extent were shown to produce the picture of a severe dementia, especially if they occupied medial areas of both thalami.

It was then concluded that the deprivation of large cortical areas, especially the granular frontal cortex, from thalamic impulses might explain the dementia. It had to be admitted that the evidence obtained from the topographic study of tumours was not sufficiently conclusive. The present case, however, presents a pure degeneration of thalamic nuclei, and is therefore more appropriate for questions of localization.

A survey of the recent work on thalamo-cortical connections (Le Gros Clark, 1936, Earl Walker, 1938) shows that not only the sensory, auditory and visual cortical areas possess a thalamic representation ; large areas of phylogenetically recent origin and highly specialized function receive direct impulses from thalamic nuclei. The physiological and clinical significance of this fact is not yet fully recognized.

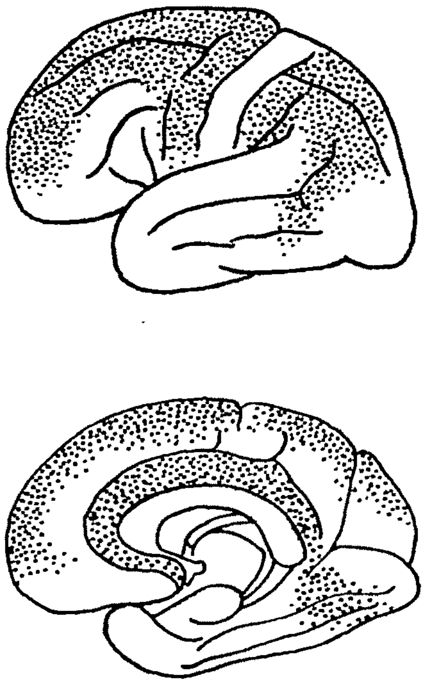

FIG. 6.—Indicates approximate extent of cortical areas which correspond to degenerated thalamic nuclei. This diagram is mainly based on recent investigations by W. E. Le Gros Clark and A. Earl Walker, quoted in text.

The present case demonstrates experimentally, as it were, the result of an isolation of vast areas of the cortex on both sides from thalamic impulses. Although the cyto-architecture of the human thalamus is somewhat different even from that of anthropoid apes one can apply the results of the above-mentioned authors to the present case. Fig. 6 gives an approximate diagram of the cortical areas which correspond to the degenerated thalamic structures. The result of this isolation was clinically identical with that of a widespread severe affection of the cortex such as general paresis or Alzheimer's disease.

A feature which distinguishes this case from common cases of presenile dementia is the marked hypersomnia which was already present at an early stage. From the patient's history it appears to be not a mere result of inertia and lack of attention, but a sleep disturbance in the strict sense.

Bailey and Fulton (1929) have remarked that it is difficult to relate hypersomnia occurring in tumours of the infundibular region to any particular structure, because the mechanical effects of pressure cannot be entirely excluded. It is, however, certain that hypersomnia, though frequent with suprapituitary tumours, occurs much more frequently in gliomas which involve the walls of the 3rd ventricle (Cushing, 1932). Ranson, Kabat, and Magoun (1935) emphasized that they were never successful in producing sleep in animals by faradic stimulation of the hypothalamus ; on the contrary, they always evoked a state of extreme emotional excitation. From this point of view it is noteworthy that all the hypothalamic nuclei were completely intact in the present case. This does not imply that the hypothalamus is not related to the function of sleep ; in fact, some of the thalamic nuclei destroyed in this case represent intermediate neurons between the hypothalamus and the cortex. Thus, the anterior nuclei receive impulses from the mammillary bodies, and the dorso-medial nucleus which projects on to the granular frontal cortex apparently receives its impulses from the hypothalamus (Le Gros Clark, 1932). The marked somnolence, therefore, so frequently combined with diseases in the region of the 3rd ventricle may be due to a lesion of the second neuron of this hypothalamo-thalamo-cortical system. The present case demonstrates at any rate that a lesion of the hypothalamus itself is not necessary to produce this symptom. A further localization is not possible because of the extent of the lesion within the thalamus.

The same disadvantage exists as far as the iridoplegia is concerned. According to Hare, Magoun, and Ranson (1935) the pretectal area, i.e. the grey formations near the ventricle immediately rostral to the superior colliculi, contains the synapses for the light reflex. These areas appear to be affected in the present case, although, as shown above, their definition is not ascertained in man. Apart from this there was a certain amount of gliosis, without any damage to nerve cells in the superior colliculi. Exact localization, therefore, of the iridoplegia in the supranuclear apparatus is not possible. It appears, however, that the present case contradicts the widely-held view that abolition of the reflex to both light and convergence is only found in disease of the peripheral neuron, for the nuclei for the intrinsic and extrinsic muscles of the eye were completely intact.

The ventral nuclei of the thalamus, which are, according to all recent anatomical reports, the only termination of secondary sensory neurons, were, except for the geniculate bodies and the mid-line nuclei, the only preserved structures of the thalamus proper. It would therefore have been of the greatest interest to obtain a picture of the sensory functions in the present case. This, however, was impossible owing to the patient's mental deterioration and complete lack of co-operation.

As far as the forced grasping and " tonic innervation " (Walshe and Robertson, 1933) are concerned, the case is of particular interest because the premotor area was intact on both sides, and the cortical changes as a whole were not sufficiently marked to account for these phenomena. This conforms with Kleist's (1927) observation that " tonic innervation " and forced grasping occur in association with thalamic lesions. It shows at any rate that these phenomena may occur when the major part of the thalamus is degenerated. It remains to be determined what is the actual mechanism of their production in a case like that here presented. Further observations may indicate whether or not they may be due to " de-afferentation " of the premotor area by the destruction of the anterior part of the lateral thalamic nucleus.

SUMMARY.

A case of severe presenile dementia with rapid course, accompanied by such neurological signs as loss of the pupillary reflexes and forced sucking and grasping movements is reported. The anatomical basis of this process was a selective bilateral symmetrical degeneration of the thalamus with exclusion of the ventral nucleus, arcuate nucleus, the mid-line nuclei, and the lateral and medial geniculate bodies. From various histological and topographical features it could be concluded that this was a peculiar system disease which has not hitherto been described. The symptomatology of the case is discussed on the basis of recent discoveries in the field of thalamo-cortical relations.

The author wishes to express his grateful thanks to Dr. J. G. Greenfield and to Dr. F. M. R. Walshe for their help and criticism, and for permission to use the post-mortem and clinical notes.

PLATE VI.

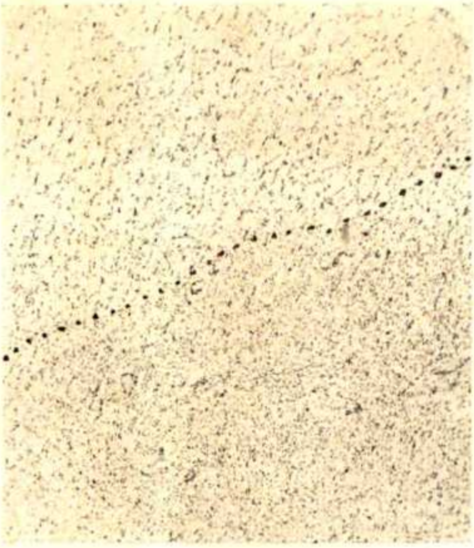

FIG. 1.

FIG. 3.

FIG. 4.

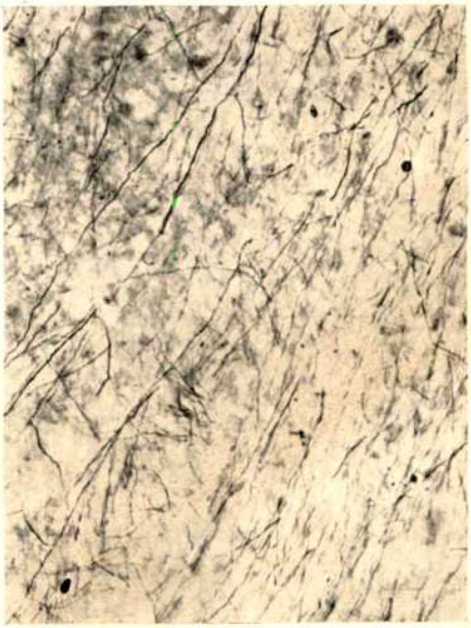

FIG. 5.

To illustrate article by K. Stern.

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LEGENDS FOR PLATE

Fig. 1.—The pulvinar and its external medullary lamina are distinguished from the internal capsule (above the dotted line) only by the density of glia. No ganglion cells are preserved. The borderline between pulvinar and internal capsule is sharp (dotted line). (Nissl.)

Fig. 3.—Borderline between ventral and medial nucleus on left side. The ganglion cells of the ventral nucleus (lower part of picture) are well preserved. Remaining part of picture shows a diffuse gliosis. (Nissl.)

Fig. 4.—Dense even gliosis without any ganglion cells in dorso-medial area of right thalamus. The cluster of preserved ganglion cells in lower right corner belongs to mid-line nuclei. (Nissl.)

Fig. 5.—Bielschowsky-Gros picture from medial area in left thalamus which in cell-stains shows a dense gliosis and complete absence of ganglion cells. Loose bundles of fine neurofibrils (probably from afferent neurons) are preserved.

NEUROGENIC HYPERTHERMIA.[1]

(A Clinical Syndrome and Its Treatment.)

BY THEODORE C. ERICKSON.
(*Montreal.*)

The term neurogenic hyperthermia is often used indiscriminately when there is disease of the central nervous system associated with an elevated temperature. For this reason it is desirable to clarify the syndrome of neurogenic hyperthermia and to answer certain questions. If there be such an entity as neurogenic hyperthermia what are its anatomical and physiological substrata, what are its clinical features, and what is its treatment ?

Descriptions of hyperthermia following brain operations have been given by Kornblum (1925), Cushing (1932), and Gagel (1936). Since the only criterion which these discussions have in common is the fact that the patient had a high temperature, we will give a clinical delineation of the cases of hyperthermia considered to be neurogenic, followed by illustrative cases, a pathological and physiological analysis and a discussion of differential diagnosis and treatment. This clinical study was carried out from 1933 to 1938.

Clinical Picture.

The clinical picture is dramatic. Most striking is the rapid rise of rectal temperature, the relative warmth of the trunk and the icy dryness of the extremities. Venous blotching often appears in non-dependent portions of the skin of the extremities and less frequently in the trunk. Pilo-erection may be present and there is complete absence of sweating (anhydrosis). Thus it is evident that heat loss is reduced to a minimum as there is no sweating, and blood flow in the skin of the extremities is greatly reduced. The patient is quiet, practically never agitated, and almost always unconscious.

Hyperpnoea is usually but not invariably an accompaniment of the hyperthermia, the respiratory rate often rising as high as 40 or 50 per minute. Sometimes there are bouts of hyperpnoea (see case 2). Tachycardia is one of the earliest characteristic signs, often occurring before the rise of temperature. A heart rate of 140 per minute is usual and in the more severe cases it rises to 180 and above. The blood pressure is often very low but may be normal. As has been pointed out by Penfield (1936) " the heart seems to be driven at such a terrific rate that in about thirty-six hours, as a rule, the patient dies of heart failure." Often the hyperthermia can be controlled while the tachycardia cannot. The electrocardiogram may show many extrasystoles ; this suggests stimulation of the posterior part of the hypothalamus (Beattie, Brow and Long, 1930).

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Decerebrate rigidity may be associated with the hyperthermia due to extension of the disturbance into the mid-brain. Neurogenic gastroduodenal ulcers occasionally occur. However, the most constant parts of the syndrome are the hyperthermia, hyperpnoea and tachycardia which suggests that their respective centres in the brain are partially co-extensive or adjacent to one another.

The syndrome of neurogenic hyperthermia is frequently observed following operative procedures on the pituitary fossa, the region of the 3rd ventricle, or the posterior fossa as well as after head injuries. The temperature rise usually occurs after general anæsthesia wears off or at least within the first twelve hours after operation or head injury. Hyperthermia (or hypothermia) is occasionally observed apart from operation with tumours involving the hypothalamus (Strauss and Globus, 1930, Davison and Selby, 1935, and others), but this is relatively uncommon.

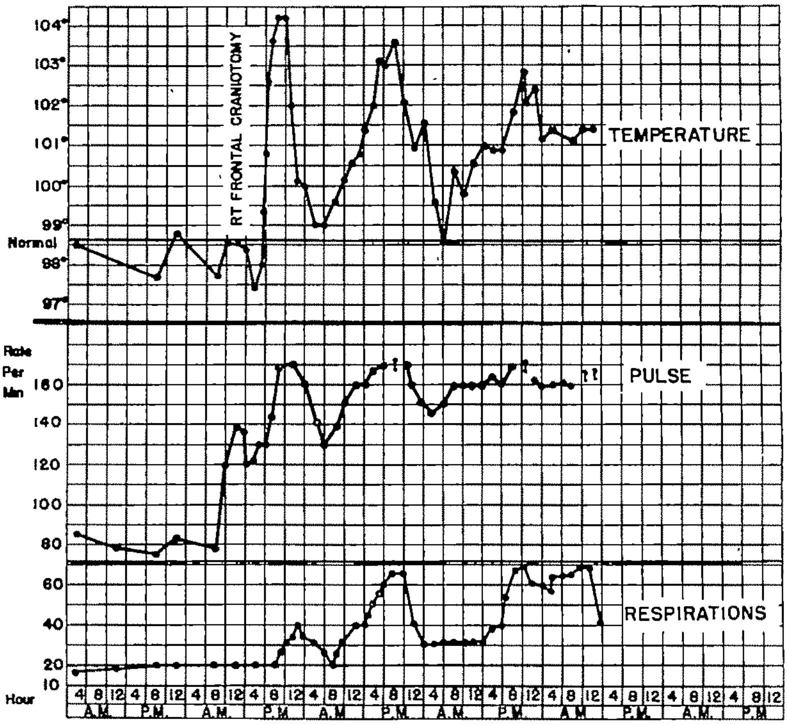
The height to which the body temperature rises is not the most important criterion of neurogenic hyperthermia, for a temperature above 105° F. usually means inadequate watchfulness on the part of those caring for the patient. If the rectal temperature be taken frequently and proper measures instituted the temperature should never go above 104° or 105° F. Although we have had patients with much higher temperatures, those we shall cite have been watched more closely and the diagnosis has been based on a concatenation of hyperthermia, tachycardia, hyperpnoea and icy dry skin rather than on a rise of temperature above some arbitrarily fixed level such as 105° F.

The following cases show some of the variants of the typical clinical picture.

Case 1.—Craniopharyngeal epithelioma, removal, post-operative hyperthermia.

S. E., female, aged 16, was admitted to the Montreal Neurological Institute, February 7, 1938, with a history of right temporal and occipital headache accompanied by nausea and vomiting of two months' duration, and failing vision of the right eye for one month. On February 11, 1938, a right frontal osteoplastic craniotomy was done by Dr. Penfield After section of the right optic nerve the tumour, which was solid, was completely removed.

On the operating table (avertin, ether anesthesia) the patient's rectal temperature varied only from 98·2° to 98·6° F. The respirations varied between 20 and 30, the pulse between 100 and 120, the systolic blood-pressure from 120 to 140 and the diastolic from 60 to 70. Within an hour following operation the temperature fell to 97·2°, blood-pressure 102/50, pulse 120, respirations 26. Four hours after operation the temperature had risen to 104·2° with blood-pressure of 88/64 and imperceptible pulse (see chart). The extremities were icy cold and dry and venous mottling appeared in the extremities and spread to the trunk. The fluid intake was adequate and the cerebrospinal fluid pressure and cytology were within normal limits. Morphine sulphate in small doses (grains 1/32) was given and resulted in an evanescent improvement. Two transfusions of 500 c.c. of citrated blood produced a temporary improvement. It was found relatively easy to lower the body temperature by physical measures adjusting the environmental temperature. The cardiac system at first responded well to this lowering of body temperature but later it did not and measures were directed toward slowing the heart, perniciously accelerated by the hypothalamic derangement. Quinidine sulphate was given. Novocain and nupercaine were injected into the stellate ganglia by Dr. Cone in the attempt to block off cardiac stimulatory fibres. Therapy was of no avail, however, and the patient died seventy-two hours after operation.



Clinical Chart Case 1.—Craniopharyngeal epithelioma, removal, post-operative hyperthermia.

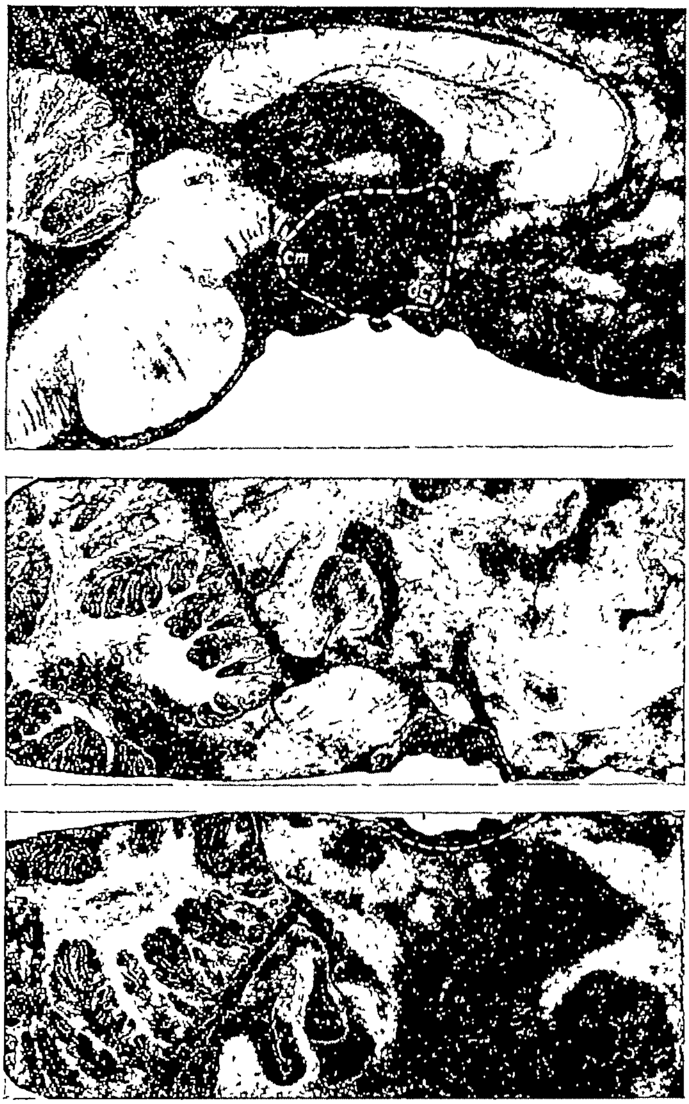
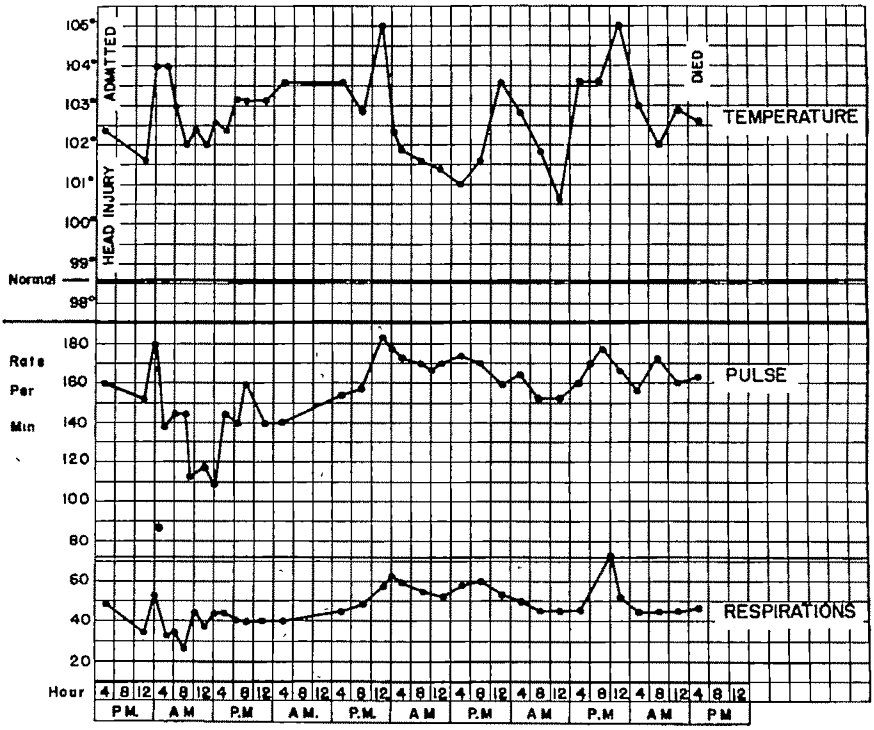


Fig. 1 —Brain sections from Case 1 (craniopharyngioma, removal, hyperthermia). A, Mid-sagittal section of the brain to show the destruction of the hypothalamus from anterior commissure and chiasma caudally through the corpora mammillaria B, C, Horizontal sections of the same to show the lateral extent of damage. The location of the lesion is outlined in dotted lines.

c.m. corpora mammillaria. o.c. optic chiasm.

Examination of the head only was allowed. The operative site was clean and free from hæmorrhage or infection. The tuber cinereum was completely destroyed (fig. 1) and there was just a hæmorrhagic remnant of the corpora mammillare on either side. The anterior commissure could not be identified with certainty. The right optic nerve was destroyed and the chiasm distorted. There was no clot in the ventricles which were not enlarged. The tumour had been completely removed. Aside from the local destruction of the hypothalamus there were no other abnormalities in the brain except for a greyish area of softening in the dentate nucleus on the left.

Comment.—Except that alert nursing care prevented a high rise of temperature the above case illustrates well the cardinal features of neurogenic hyperthermia. The fact that the temperature fell below normal at first suggests that the mechanism of heat production was impaired as well as that of heat elimination, as will be discussed later. The tremendous acceleration of heart rate and the vascular changes responded only temporarily to blood transfusion, which helps to distinguish this from a case in which there has been much blood loss and the problem is merely one of restoring blood volume.



Clinical Chart Case 2.—Head injury, hyperthermia, paroxysms of hyperpnoea, focal hæmorrhages in the hypothalamus.

Case 2.—Head injury, hyperthermia, focal hæmorrhages in hypothalamus. H. A., aged 23, was admitted to the Royal Victoria Hospital, September 15, 1933, shortly after being hit by a car. He was unconscious with a fixed dilated pupil on the left and accentuated tonus and deep reflexes on the right. Paroxysmal attacks of hyperpnœa occurred shortly after admission with respirations increasing gradually to 48 and pulse to 160 but regular. With each paroxysm the face and neck were covered with perspiration that collected in pools in the eye sockets and neck, but from the nipples down he was dry and hot. There was shivering of the whole body and the legs were in extensor spasm, the right more rigid that the left. The left arm was flexed and the right extended. These paroxysms of hyperpnœa, etc., were set off by any slight stimulus just as in strychnine poisoning. Morphine sulphate (grains 1/32) in repeated doses and sodium amytol produced slight temporary improvement. Blood chlorides, CO_2 capacity and total protein N were within normal limits. Three days after admission the patient showed signs

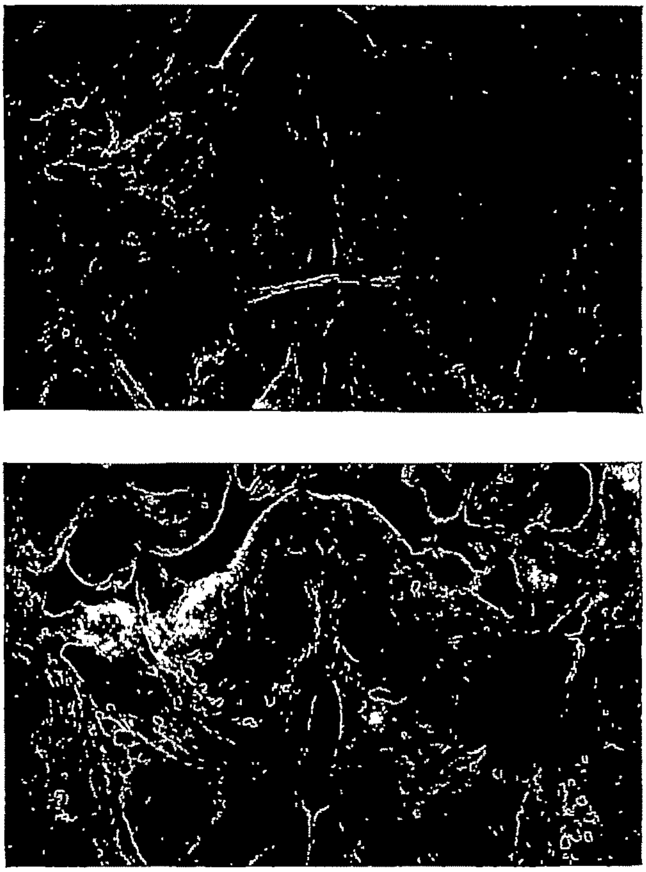
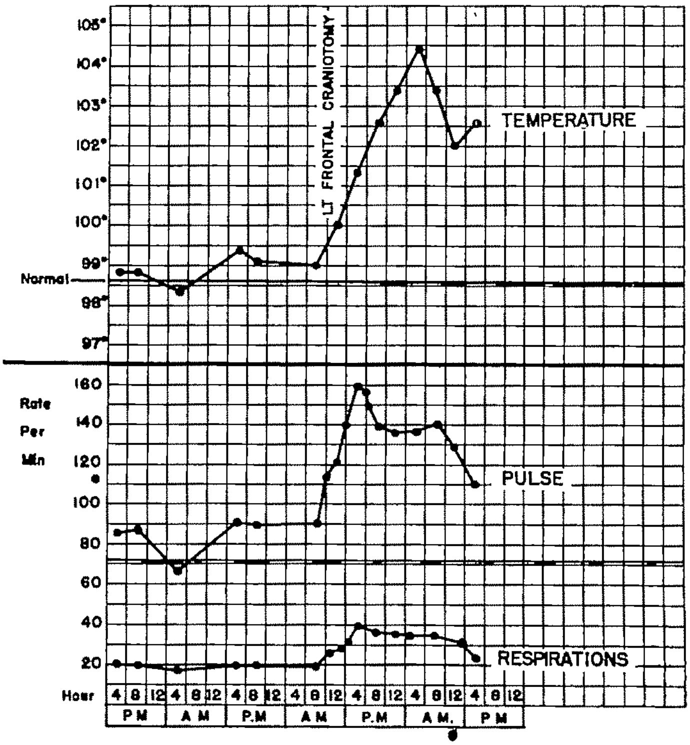


FIG. 2—Horizontal sections through hypothalamus and mid-brain of Case 2. This shows the extent of the hæmorrhage in the hypothalamus in a case of hyperthermia following head injury.

of pulmonary consolidation and he died five days after the injury. The summary of the post-mortem findings was as follows: diffuse bronchopneumonia of the base of the left lung, diffuse punctate hæmorrhages of the cerebrum, pons and medulla, cortical adenoma of the adrenal, focal fibrosis and calcification of the spleen, and a recent lacerating wound of the scalp. On cutting the brain, discrete areas of hæmorrhage were observed in the corpus callosum, the fornix, the hypothalamus and the mid-brain (fig. 2). All except the tuber group of nuclei were involved on one side for the hæmorrhage extended obliquely to the section. Posteriorly it extended between the nuclei rubra to within 6 mm. of the aqueduct.

Comment.—Obviously the bronchopneumonia was terminal and did not account for the initial high temperature which was undoubtedly neurogenic in origin. The paroxysmal discharges were evidently due to irritation of centres for sweating, respiration, heart beat, standing rigidity and shivering. This presents a far more complex physiological picture than the usual case of the kind. It serves, however, to emphasize the fact that body temperature is intimately related to various organic processes and is the algebraic sum of these various functions which are each under the control of hypothalamic centres.

Case 3.—Meningeal fibroblastoma, removal, hyperthermia. B. A., female. aged 32, was admitted March 7, 1930, and on March 18 a left frontal osteoplastic

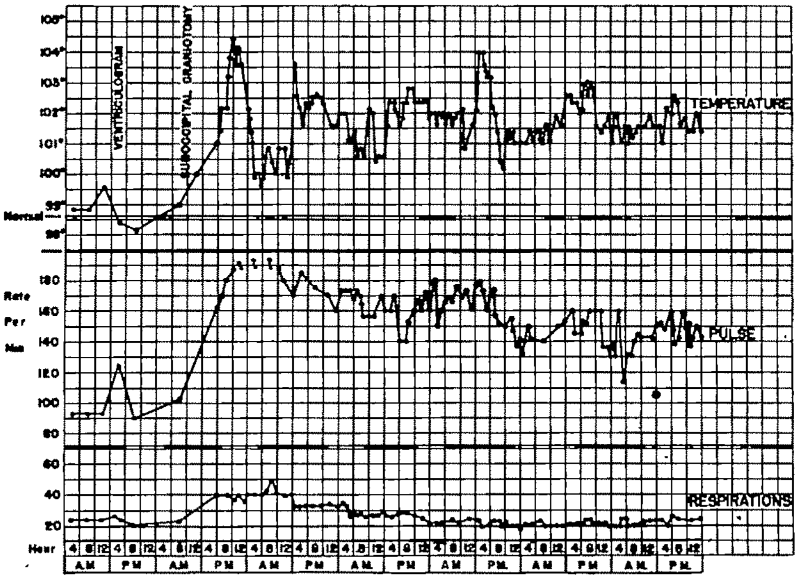


Clinical Chart Case 3.—Meningeal fibroblastoma, removal, hyperthermia.

craniotomy was performed. The tumour, a meningeal fibroblastoma arising from the olfactory groove, was completely removed by Dr. Penfield. As the wound was being closed the respiratory rate rose to 40 per minute and the pulse to 140. The rectal temperature rose rapidly to 104·4°. She failed to regain consciousness and died 24 hours after operation. Post-mortem examination showed definite congestion of the head of the caudate nucleus and anterior half of the putamen on the left side; the area supplied by the artery of Heubner. No gross abnormality was seen in the hypothalamus or elsewhere in the brain. The lesion in the corpus striatum appeared to be due to thrombosis of the anterior cerebral artery, or its branch, the artery of Heubner, perhaps secondary to retraction or to the use of the electrocautery.

Comment.—In this clinical case the hyperthermia resembles the " heat punctures " of Aronsohn and Sachs (1885), Wood (1880), Ott (1884), and others, because of the situation of the pathological lesion. Aronsohn and Sachs observed a rise of temperature within two to four hours after a lesion involving the head of the corpus striatum and the basis cranii (rabbits and dogs). In none of our other clinical cases has the pathological lesion involved the region of the head of the corpus striatum.

Case 4.—Glioma arising from quadrigeminal plate, removal, hyperthermia, recovery. I. B., male, aged 9, was operated on January 25, 1934. Through a suboccipital craniotomy Dr. Cone removed a glioma (unclassified) from the roof of the fourth ventricle and mid-brain. Immediately the extremities became cold and



Clinical Chart Case 4.—Glioma arising from the quadrigeminal plate, removal, hyperthermia, recovery.

dry, the temperature rose to 104·6°, the respiratory rate varied between 40 and 50 per minute and the pulse was over 150 with much irregularity (extrasystoles). Removal of bed clothes, alcohol sponges, the use of an electric fan, and repeated doses of aspirin and morphine caused an improvement and the patient finally left the hospital March 2, 1934. He was still living and well in August, 1938. Chart 4 shows the typical clinical chart during the immediate post-operative period.

Comment.—The operative approach was so strictly localized in the posterior fossa that no other mechanism for the hyperthermia can be suggested in this case than a lesion of ascending or descending thermotaxic fibres in the mid-brain or medulla. Although the tumour was limited to the corpora quadrigemina the operative approach may have produced œdema ventral to the aqueduct of Sylvius as well.

PATHOLOGICAL ANALYSIS.

Twenty autopsy specimens from patients with neurogenic hyperthermia were studied. In sixteen of these there were definite gross lesions in the hypothalamus or in the brain-stem where they could involve experimentally demonstrated heat-regulatory centres or pathways. The extent and distribution of some of these lesions is shown in fig. 3. The hypothalamus was directly involved in seven instances. Fig. 3 emphasizes the distribution of cases and not the concentration, i.e. two out of seven lesions in the hypothalamus are indicated while the one lesion in the quadrigeminal plate is shown.

The typical syndrome sometimes occurs in the absence of direct gross involvement of the hypothalamus as in the patient with removal of a tumour from the quadrigeminal plate (see Case 4). This patient did not die so it is impossible to say that he did not have small hæmorrhages or œdema of the hypothalamic centres. In Case 3 there was softening of the cranial part of the corpus striatum due to thrombosis of the artery of Heubner without any evident lesion in the hypothalamus. The area involved is comparable to that of the "heat punctures" of earlier authors such as Aronsohn and Sachs and may be homologous to the region which is active in heat loss in the cat, as demonstrated by Magoun *et al.* (1938). In this instance both the pathological and physiological findings agree in explaining the hyperthermias on a basis of paralysis of the central mechanism concerned in heat loss. With extensive destruction of the hypothalamus, particularly of the anterior portion as in Case 1 (cf. fig. 1), the same explanation would hold. The persistent tachycardia in Case 1 is apparently related to a release of cardiac acceleratory centres in the posterior part of the hypothalamus.

The scattered focal hæmorrhages in the hypothalamus which were found in Case 2 (cf. fig. 2) are especially interesting in view of the atypical accompaniments of the hyperthermia. Anhydrosis and icy dry skin were observed only below the nipples while above there was profuse perspiration. This suggests that there had been a selective paralysis of some heat-loss mechanisms with stimulation of others. In the same way may be explained the bouts of hyperpnoea which some patients have at intervals.

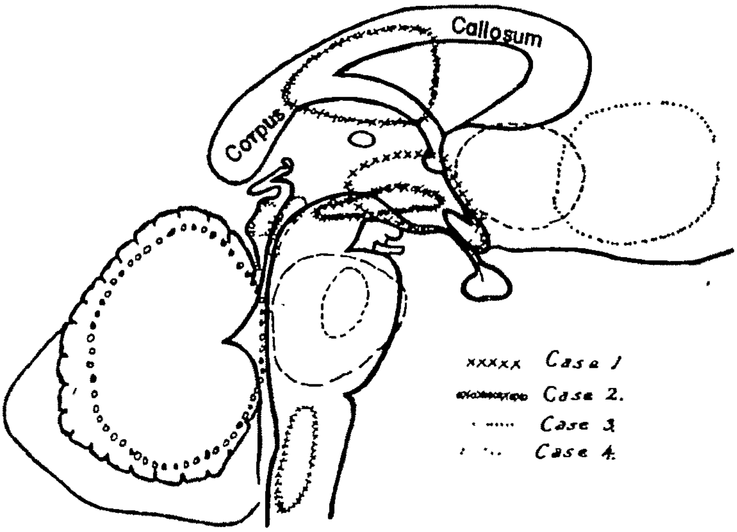


Fig 3.—Diagram of the brain-stem to show distribution of some of the pathological lesions in cases of hyperthermia. The scatter confirms the conception that the reflex arcs concerned in temperature regulation are widely spread in the brain-stem.

Pathological material from the following cases has been studied as well as from those cases which have been discussed in detail previously.

S. G.—Perineurial fibroblastoma of right 12th cranial nerve with hæmorrhages in the medulla.

C —Perineurial fibroblastoma of the 8th cranial nerve ; petechial hæmorrhages on the left side of the pons.

M. H.—Cyst of medulla ; cystic arachnoiditis in posterior fossa, sagittal sinus thrombosis

M. W.—Massive tumour (astroblastoma) involving both frontal lobes and extending back to the mid-brain.

C. W.—Cerebral concussion, contusion and laceration ; one area of hæmorrhage in posterior part of third ventricle.

R. H.—Astroblastoma of optic chiasma extending through the hypothalamus to the pons.

J. S.—Diffuse brain injury—third ventricle grossly normal but slight congestion of left putamen.

M. D.—Medulloblastoma—right cerebellar hemisphere.

E. Q.—Hæmorrhage in the temporal lobe—third ventricle normal.

H. T.—Head injury—third ventricle and basal ganglia normal.

B O.—Cerebral concussion and subarachnoid hæmorrhage, punctate hæmorrhages in wall of third ventricle extending from the lamina terminalis three-quarters of the way back to the corpora mammillaria.

F. O.—Midline cerebellar hæmangioma—hæmorrhage around the aqueduct of Sylvius.

Th.—Bilateral frontal astroblastoma—hæmorrhage just anterior to the lamina terminalis.

Ca.—Meningeal fibroblastoma of right middle fossa extending to the midline and into the posterior fossa.

Fe.—Diffuse brain injury with intracerebral and subarachnoid hæmorrhages but no localization in diencephalon.

Bo.—Infiltrating tumour of the pons extending from the floor of the 4th ventricle to the basilar artery.

Pa.—Extensive infiltration and softening of the left temporal lobe, basal ganglia and third ventricle.

These, together with fig. 3, illustrate that hyperthermia occurred most frequently when the hypothalamus or the brain stem at lower levels was involved.

It is evident that the lesions, although diverse as to histology, have a certain common denominator, i.e. either proximity to or actual involvement of regions most concerned in thermotaxis in the hypothalamus or their pathways in more caudal parts of the brain stem. A consideration of experimental physiological studies is necessary for further interpretation.

Physiological Analysis.

Body temperature is the product of several physiological processes (fig. 4) which may be grouped into those concerned with heat production (chemical regulation) and those concerned with heat elimination (physical regulation). Eighty per cent. or more of body heat is produced in the muscles (and glands). Since the greater part of heat production occurs in the deeper parts of the body the first stage in heat elimination is shift of heat to the surface where it may be lost (indicated in fig. 4 by dotted lines) (for our present purposes we may ignore the quantitatively insignificant rôle of the excreta and respiration in heat loss in man). This is accomplished in two ways, first by direct conduction of heat through the tissues, and second by internal convection of heat by means of the blood stream. Convection of heat by the circulating blood is used in a sense analogous to convection of heat in a liquid or air, i.e. transference of heat from place to place by actual motions of the hot body. When the heat finally has reached the skin its loss becomes a purely physical process (Burton, 1934)

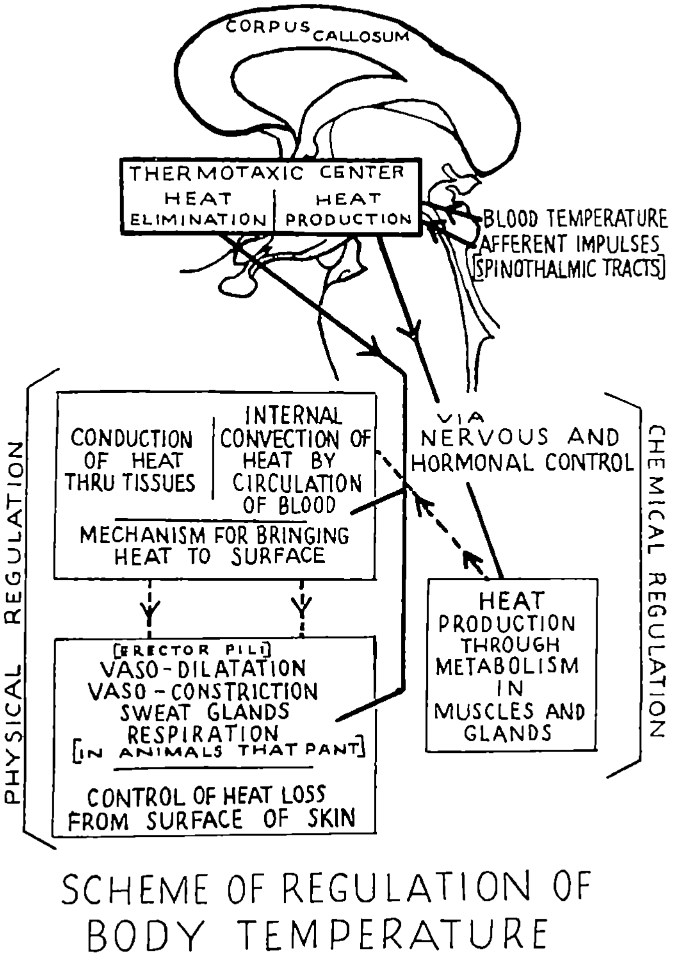

CORPUS CALLOSUM
THERMOTAXIC CENTER
HEAT ELIMINATION
HEAT PRODUCTION
BLOOD TEMPERATURE
AFFERENT IMPULSES
[SPINOTHALMIC TRACTS]
CONDUCTION OF HEAT THRU TISSUES
INTERNAL CONVECTION OF HEAT BY CIRCULATION OF BLOOD
MECHANISM FOR BRINGING HEAT TO SURFACE
[ERECTOR PILI]
VASO-DILATATION
VASO-CONSTRICTION
SWEAT GLANDS
RESPIRATION
[IN ANIMALS THAT PANT]
CONTROL OF HEAT LOSS FROM SURFACE OF SKIN
VIA NERVOUS AND HORMONAL CONTROL
HEAT PRODUCTION THROUGH METABOLISM IN MUSCLES AND GLANDS
PHYSICAL REGULATION
CHEMICAL REGULATION
SCHEME OF REGULATION OF BODY TEMPERATURE

Fig. 4.—Scheme of regulation of body temperature. Dotted lines indicate the course of heat flow in the body while solid lines indicate the nervous factors in thermotaxis. Upward arrows indicate stimulating factors of hypothalamic centres and downward arrows projection fibres to lower centres.

controlled by sweating and vasomotor changes. Apart from pointing out the prominent part played by the vasomotor responses in the amount of heat loss from the skin, further consideration of the peripheral mechanism in heat regulation is beyond the scope of this paper. The reader is referred to the reviews of Barbour (1921), Isenschmid (1926), Bazett (1927), and Deighton (1933), as well as to the excellent paper of Burton.

A well established fact is that in the hypothalamus, at the level of the mammillary bodies, there is a region the preservation of which is essential to maintenance of normal heat regulation or thermotaxis.[1] (Isenschmid and Krehl, 1912, Isenschmid and Schnitzler, 1914, Bazett and Penfield, 1922, Bazett, Alpers and Erb, 1933, Erickson, 1934, and others.) A decerebration at the collicular level in cats and which passes below this thermotaxic centre is followed by a condition of poikilothermia, the temperature varying directly with that of the environment as with cold-blooded animals. Ranson (1935) and his co-workers have localized the region more laterally by means of lesions produced with a Horsley-Clarke apparatus. However, the reflex arcs concerned in thermotaxis must be more widespread than this, as shown by the old experiments on heat puncture: Richet (1885), Aronsohn and Sachs (1885), Ott (1884, 1914) and the newer observations of Ranson and his co-workers (1937), of Pinkston, Bard and Rioch (1934), and others.

A priori, we should not expect to find a sharply localized centre for thermotaxis since body temperature is the algebraic sum of other variables, such as cutaneous vasodilatation, general metabolism, water-metabolism, respiration, etc. Of course there may be one thermostat presiding over these various body functions as they affect body temperature. However, all the evidence, both clinical and experimental, is against such a precisely localized area. Ranson and Ingram (1935) have shown that the heat regulating centre in the posterior part of the hypothalamus is really concerned in heat production, in guarding the body against heat loss. Some authors have suggested that a parasympathetic centre in the anterior hypothalamus is concerned in heat elimination and a sympathetic centre in the posterior hypothalamus has to do with heat production. A centre for heat elimination between the anterior commissure and the base of the brain and extending back in the dorsal part of the hypothalamus has been demonstrated by Magoun *et al.* (1938). By local heating of the animal brain, with low voltage, high-frequency currents passed between electrodes oriented by the Horsley-Clarke apparatus, they obtained acceleration of respiratory rate, panting, and sweating of the foot pads.

Normally stimulation of these thermotaxic centres may be produced, either by changes in blood temperature or by afferent nervous impulses

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[1] Thermotaxis is used to designate the mechanisms concerned in the adjustment of body temperature in preference to that word of dual etymological derivation, " thermoregulation."

(anterolateral column, spinothalamic tracts), Greving (1931), Pickering (1931), Jung, Doupe and Carmichael (1937). Isenschmid and Schnitzler (1914) stated that efferent thermotaxic fibres are widely scattered in the ventral portion of the brain-stem. Foerster (1936) stated that in the cervical cord these fibres are localized in the anterolateral portion, basing this opinion on the occurrence of hyperthermia following section of the spino-thalamic tracts.

Neurogenic hyperthermia cannot be said to have been reproduced experimentally, for "heat puncture" is only a fragment of the whole picture (Erickson, 1934). The slight hyperthermia following a lesion in the anterior hypothalamus of animals (Teague and Ranson, 1936) is due to lack of panting when exposed to high environmental temperatures. At best a composite picture may be constructed from the results of different experiments on the hypothalamus. This difference between man and the lower animals: that is, in the appearance of neurogenic hyperthermia, may be explained by quantitative differences in the manner of heat loss. In man heat loss occurs mainly by way of the skin, but in the usual laboratory animals the respiratory tract plays a much larger part. Theoretically hyperthermia may be due to decreased heat elimination, increased heat production or a combination of the two as a result of a lesion affecting such centres. From the clinical picture, neurogenic hyperthermia seems to be due largely to a decrease of heat loss.

In those instances in which no gross lesion was demonstrable in the hypothalamus there may have been circulatory alteration in the hypothalamus. An inadequate circulation in the hypothalamus might, by local lowering of temperature, induce a vicious cycle because of lack of stimulation of a heat loss centre. The work of Barbour and of Magoun *et al.* furnish an experimental basis for such an explanation.

DIFFERENTIAL DIAGNOSIS.

Neurogenic hyperthermia may be simulated by hyperthermia due to many other causes which may be classified as follows:—

A CLINICAL CLASSIFICATION OF HYPERTHERMIA.

I. Hyperthermia due to Infection.

II. Hyperthermia due to Failure of Heat Elimination (not neurogenic) particularly internal convection.

- (*a*) Inadequate circulation.
- (*b*) Anhydremia. This may be produced by:—
  - (1) Excessive hypertonic injections.
  - (2) Low fluid intake.

III. Neurogenic Hyperthermia (in broadest sense but disregarding drugs and toxins which act on hypothalamic centres).
  (*a*) Spinal Poikilothermia (Hyperthermia or hypothermia).
  (*b*) Central Poikilothermia due to Inhibition or Paralysis of Thermotaxic centres.
    (1) Anæsthesia.
    (2) Acutely increased intracranial pressure.
  (*c*) Neurogenic (Central or hypothalamic) Hyperthermia.

Even the elevated temperature of infections may be due to the effect of toxins on the hypothalamic centres (Citron and Leschke, 1913) and so be fundamentally neurogenic in origin. In the mind of the general surgeon elevated temperature is almost synonymous with infection and rightly so. The same should be true in dealing with the nervous system, but other causes must more often be considered. If the temperature rises shortly after a brain operation or injury neurogenic hyperthermia must be considered for the temperature elevation of infection occurs only two or three days later.

The circulation of blood plays a part in heat elimination by acting as an agent for the internal convection of heat, i.e. transporting the heat from the locus of production to the surface where it can be eliminated by radiation or evaporation. A poor circulation of blood may decrease metabolism and thus decrease heat production, leading one to expect a lowering of body temperature, but the interference with heat elimination by curtailment of internal convection is quantitatively greater than any effect on heat production. It has been shown that the mechanisms operative in chronic cardiac failure may produce a fever (Cohn and Steele, 1934). Acute circulatory insufficiency may produce a rise of temperature in the same way by inadequate internal convection of heat and by concomitant cutaneous vasoconstriction. It is an old saying that people with poor circulation have cold hands and cold feet and the same holds true for patients with neurogenic hyperthermia.

Anhydræmia such as produced by a combination of low fluid intake and injection of excessive hypertonic solutions may lead to an elevated temperature as was demonstrated experimentally by the work of Balcar, Sansum and Woodyatt (1919). In neurosurgical cases where hypertonic solutions are commonly used to reduce increased intracranial pressure this may occasionally contribute to a rise of temperature.

A normal man maintains his body at a more constant temperature than any of the lower animals. He is a more perfect homotherm than any of the animals studied in the laboratory but even he may, under certain abnormal conditions, become poikilothermic with a body temperature which varies directly with that of the environment. This effect may be partial or complete. The poikilothermia, which is caused by a lesion of the cervical or high thoracic region of the spinal cord (Gardiner and Pembrey, 1912), is usually manifest as a hyperthermia because most good hospitals protect their patients against heat loss all too well. However, from the same lesion under conditions of military surgery a low temperature may be the rule (Gordon Holmes, 1915).

In a series of 15 cats it was found that acutely increased intracranial pressure may cause a poikilothermia (unpublished experiments by the author). An increased or a decreased temperature resulted, depending upon the thermal environment in which the experiments were performed. Clinical confirmation of this effect of acute increase of intracranial pressure was furnished by study of a group of cases with hæmorrhage from the middle meningeal artery. On admission these cases showed either a high, a low, or a normal temperature depending upon the environmental temperature to which they had been exposed prior to admission. After being cared for in the hospital their temperatures were always high or normal, such as one would expect with inhibition of thermotaxic centres. Not infrequently such cases are complicated by the presence of intracerebral hæmorrhages involving the thermotaxic centres or pathways, thus producing a positive hyperthermia.

Any general anæsthetic, whether it be avertin, ether or the barbiturates causes a marked derangement of the thermo-taxic centres. The fact that patients, during and after general anæsthesia, are sensitive to cold has long been emphasized in the minds of the best nursing and resident staffs but the fact that they are just as susceptible to excessive heat is often not realized. It used to be a common occurrence several years ago, before the nursing staff was centralized and especially trained, to have the patient, upon leaving the operating room with a normal or slightly elevated temperature, put in a preheated bed with hot water bottles and three or four heavy blankets. These patients, from no other cause, would develop symptoms closely simulating neurogenic hyperthermia. If they had the pathological and physiological substrata of a neurogenic hyperthermia, coals were added to the fire.

What may be called the momentum of a rising body temperature may cause a very deceptive clinical appearance. This may be readily demonstrated in the laboratory. A cat which has been rendered poikilothermic by a low decerebration and which has a rising rectal temperature because of a high environmental temperature continues to show a rise of temperature for a short interval of time after removal of the external heat. Similarly a patient with a rising temperature may show a continued rise of temperature for a short time after exposure to a cooler environment. This does not necessarily mean that there is an active or positive neurogenic hyperthermia. A rising temperature is part of a vicious cycle, increased body temperature increases metabolism by increasing the velocity of the chemical reactions and the increased heat thus produced raises, in turn, the temperature.

TREATMENT.

Once fully developed, neurogenic hyperthermia presents a serious outlook. Tepid sponges, ice-water enemas and ice-bags can be used if removal of covers from the patients and lowering of room temperature are not effective. In a true neurogenic hyperthermia local application of heat does not produce a vasodilatation of the cold dry extremities. By repeated small doses of morphine (grains 1/32 or 1/64) together with the usual physical measures for lowering temperature, some ground may be gained. This helps to quiet the hyperpnœa and tachycardia and tends to cause vasodilatation, rendering cooling applications to the skin more effective. Aspirin, though less effective, seems to be of use when given in large doses.

Other measures, some with effect, have been tried in isolated cases. Cushing reported that intraventricular pituitrin caused a fall of temperature in one case of neurogenic hyperthermia. Local application of carbon dioxide to the skin in a suitable form might be effective in dilating the skin vessels and promoting cooling (Bazett). Drugs such as physostigmin and acetyl B methyl choline (mecholyl) have been tried but are limited in use because of their effect on the blood-pressure. These patients are more sensitive than normal to mecholyl, which in itself is significant. Minute doses of mecholyl may, however, be of distinct use. Tachycardia is often one of the most prominent features and death is caused by a circulatory failure. Various measures have been used to slow the heart, such as quinidine and injection of the stellate ganglia, but without uniform success. Needless to say one should always be sure that the fluid intake is adequate. *Transfusion is often indicated and should be done in the early stages.*

It is to be emphasized that neurogenic hyperthermia, as well as other hyperthermias, may be prevented or at least alleviated *by close routine attention to the patient's rectal temperature in relation to his thermal environment.* This is necessary mainly in the immediate post-operative or post-traumatic period, when readings should be taken every half hour. Following operation on the hypophysis, the third ventricle, or the posterior fossa even a small rise of temperature above 100° should be a signal for removing the bed coverings from the patient. If the rise continues in spite of this the room temperature should be lowered, air movement should be increased by use of a fan and if necessary alcohol sponges and ice water enemas, etc., should be instituted. Aspirin in large doses and morphine in small doses are then used.

To illustrate the effectiveness of these simple routine procedures, we may say that during the two years preceding July, 1934, before these measures were first instituted, there were at least 21 cases which were diagnosed as neurogenic hyperthermia. In the four years since these measures have been closely followed, there have been only five.

SUMMARY AND CONCLUSIONS.

The syndrome of neurogenic hyperthermia is discussed on the basis of observations of clinical cases, of studies on pathological specimens and on experimental work. The differential diagnosis and treatment are outlined.

From this study the following conclusions may be drawn.

(1) Neurogenic hyperthermia is manifested by a high internal temperature and icy cold dry skin occurring shortly after head injury or operation in the region of the 3rd ventricle or posterior fossa, and less frequently pre-operatively with tumours in the diencephalon. The patient is unconscious, the respiratory and pulse rates are usually very high and the outcome is often fatal.

(2) Body temperature is the algebraic sum of the functions of the heart and general circulation of blood, of the general metabolism, of the cutaneous vasoconstriction and vasodilatation, and of the rapidity of respiration. For this reason the manifestations of neurogenic hyperthermia may vary inasmuch as variable portions of the neuronal centres and pathways directly or indirectly concerned with heat regulation are affected by the lesion.

(3) Prophylactic measures are genuinely effective in lowering the incidence and mortality from neurogenic hyperthermia.

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THE SENSORY INNERVATION OF THE SPINAL ACCESSORY AND TONGUE MUSCULATURE IN THE RHESUS MONKEY.

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THE peripheral portion of the spinal accessory nerve in the cat carries proprioceptive fibres from the accessory muscles (sternomastoid, cleidomastoid and trapezius) (Corbin and Harrison, 1938; Echlin and Propper, 1938). By means of the cathode ray oscillograph and degeneration experiments, we have found that these proprioceptive fibres enter the central nervous system by way of the peripheral anastomoses of the upper five cervical ventral rami with the spinal accessory nerve, and therefore have their cells of origin in the respective dorsal root ganglia (Corbin and Harrison, 1938). Similar studies on the rabbit reveal that the 3rd and 4th cervical spinal nerves, joining the accessory nerve in the neck, carry the muscle sense fibres from the accessory muscles in this animal (Yee, Harrison and Corbin, 1939). In neither the cat nor the rabbit could action potentials indicative of proprioceptive activity be obtained in the portion of the spinal accessory nerve immediately external to the jugular foramen (therefore proximal to the anastomoses of the ventral rami with the accessory nerve) during stretch of the accessory musculature, although this stimulus regularly evoked such potentials in the more peripheral portions of the accessory nerve and various cervical ventral rami. Hence in these animals the intracranial and intraspinal portions of the spinal accessory nerve are primarily motor. While admitting that impulses arising in the more caudally situated accessory muscles (trapezii) in the cat probably pass centrally over the cervical ventral rami, Tsuruyama (1938) believes that proprioceptive impulses from the rostrally located muscles (sternomastoid and cleidomastoid) pass centrally with the accessory and "nach dem Eintritt ins Marks intramedullär zur hinteren Wurzel sich begeben, . . ." Certainly our experiments indicate little need for such an explanation.

In the cat and rabbit, faradic stimulation of the peripheral stumps of the cut upper five cervical ventral rami never produced contraction of the accessory muscles. Accordingly in these animals it would appear that the accessory musculature receives its entire motor innervation through the spinal accessory nerve. Similarly in the following experiments we have found that the accessory musculature in the monkey receives its entire motor innervation through the spinal accessory nerve and its sensory supply from the dorsal root ganglia of C.2, C.3, and C.4, via the respective cervical ventral rami and their peripheral anastomoses with the accessory nerve.

Corbin, Lhamon and Petit (1937) found a small number (1 per cent. to 5 per cent.) of degenerating fibres in the most peripheral portion of the hypoglossal nerve after removal of C.2 dorsal root ganglion in the monkey. This suggested an extracranial contribution of sensory (probably proprioceptive) fibres to the tongue musculature from this ganglion. A similar contribution from C.1 dorsal root ganglion to the muscular portion of the hypoglossal nerve was found in the rabbit by Yee, Harrison and Corbin (1939).

Although Carleton (1938) found no muscle spindles in the rabbit tongue, she reported complete degeneration of interstitial and epilemmal terminals in the tongue following section of the hypoglossal nerve. Such terminals were present after section of the lingual nerve. Similar observations were made by Corbin and Yee (unpublished) on the cat and monkey tongue using a methylene blue technique. This is contrary to what one would expect from the work of Barron (1936) but agrees with our physiological results (1938) in which we found tactile but no proprioceptive impulses in the lingual nerve upon stretching or twisting the tongue. No evidence for a sensory contribution from the upper cervical dorsal root ganglia to the hypoglossal nerve was found in the cat (Hinsey and Corbin, 1934 ; Barron, 1936 ; Corbin and Harrison, 1938).

Material and Methods.

Fourteen adult Macacus rhesus monkeys were used in this study. All operative procedures were carried out under intravenous sodium pentobarbital anesthesia. Using the cathode ray oscillograph and loud speaker we traced action potentials, elicited through stretch of the accessory muscles, through various branches of the accessory nerve and the cervical ventral rami. Accessory muscles were isolated except for their nerve supply and rostral attachments. Recording leads consisted of two 26 gauge silver wires chlorided electrically and separated from 1 to 3 mm Potentials were amplified by a three stage resistance coupled amplifier. An output of 10 u V. gave a deflection of 1 cm. on the screen at the highest amplification used. The usual precautions to avoid extraneous impulses were observed (Adrian, 1930) The peripheral stumps of the upper five cervical ventral rami were tested with bipolar faradic stimulation in those animals which were used for oscillographic studies. Stimulation was through platinum electrodes with a tip separation of 2 mm.

Histological experiments in which the upper five cervical ventral rami were divided in various bilateral combinations were also carried out (See table). Following adequate degeneration time, usually 7 days, the various nerves studied, including various portions of the twelfth cranial nerve, were removed and placed in 1 per cent. osmic acid for 24 hours. They then were carefully teased in glycerine and examined for degeneration. The direct osmic acid method has proved of much greater value to us for the study of degeneration in peripheral nerves than the Marchi method.

TABLE SHOWING VARIOUS NERVES DIVIDED.

Monkey No.		801	802	803	804	805	806
Spinal nerve (Ventral ramus) divided	Left	C.3	C.4	C.2[1]	C.3	C.4	C.2[1]
	Right	C.2	C.4	C.3	C.2	C.2	C.2[1]

[1] Only the rostral branch of C.2 to the hypoglossus was divided.

RESULTS AND DISCUSSION.

The anastomoses between the upper cervical ventral rami and the accessory nerve in the monkey have been described by Tanaka (1932), Christensen (1933) and Corbin, Lhamon and Petit (1936). The most frequent type of anastomosis is illustrated in the diagram in which we have also indicated the course of the sensory fibres to the accessory muscles.

Stretching of the inferior trapezius muscle regularly elicited proprioceptive action potentials (as defined by Matthews, 1933; and Corbin and Harrison, 1938) in that portion of C.4 ventral ramus which communicates with the accessory nerve, occasionally in C.3 ventral ramus. Impulses initiated through stretch of the superior trapezius passed centrally over branches of the ventral rami C.2, C.3 and C.4 which anastomose with the accessory nerve. Stretching of the sternocleidomastoid group uniformly elicited action potentials from C.2 and C.3 ventral rami, but never in C.4 ventral ramus.

When the peripheral end of the cut spinal accessory nerve (just external to the jugular foramen) was placed on recording leads, an increase in the amplitude and frequency of action potentials was noted on stretching the sternocleidomastoid muscle. This activity did not appear when the branch to this muscle from the accessory was cut. No such response was elicited by stretching the trapezii, although stretching the latter muscle evoked a marked response in those portions of the accessory peripheral to the anastomotic branches of C.3 and C.4. Because the monkey's neck is short, the length of the accessory nerve between the jugular foramen and the sternomastoid muscle is less than in the cat and rabbit. It is therefore difficult to place this portion of the nerve on the leads without including those fibres from C.2 and C.3 which enter the branches to the sternomastoid and cleidomastoid muscles. We feel that this is probably the explanation for our obtaining responses from this portion of the accessory nerve in the monkey whereas the same portion of this nerve was silent in the cat and rabbit. In view of our results in the latter animals we believe it unlikely that any proprioceptive fibres from the sternomastoid muscle pass intracranially in the accessory nerve. However, the latter possibility certainly exists, and if so, such fibres may have their cells of origin in those small ganglia occasionally found along the course of the spinal accessory (Weigner, 1901; Streeter, 1905; Fahmy, 1927; Windle, 1931) or in the upper cervical dorsal root ganglia, to be reached by intraspinal anastomoses between the accessory and the dorsal roots (Kazzander, 1891; Weigner, 1901; Streeter, 1905; Pearson, 1937). We have been unable to find such anastomoses in our studies of the cord and accessory nerve in the monkey.

As in the cat and rabbit, stimulation of the peripheral ends of the cut cervical ventral rami of the monkey never caused contraction of the muscles innervated by the spinal accessory nerve. Strauss and Howell (1936) obtained "weak though definite action of the trapezius," in one chimpanzee from stimulation of the peripheral stump of a branch from C.3 and C.4 spinal nerves to the accessory. However, since we have never observed such contraction, we conclude that any degenerating fibres found in the accessory nerve following section of the ventral rami must be sensory in nature.

In all cases the medium—large-sized myelinated fibres were the type found to be degenerating. Section of C.2 ventral ramus led to degeneration of a large number of fibres in the accessory branches to the sternocleidomastoid muscles. A smaller number of fibres from C.2 continued in the accessory supplying the trapezius muscles. Section of C.3 ventral ramus resulted in degeneration of a large number of fibres in the branches to the sternocleidomastoid muscles and in the peripheral portion of the accessory and its branches to the trapezii. Following section of C.4 ventral ramus, degenerating fibres were followed peripherally in the accessory through its various branches to the trapezii but no degenerating fibres passed to the sternocleidomastoid muscles. The results of the oscillographic and degeneration experiments are summarized in the diagram, in which it should be noted, that the anastomotic branches between the cervical ventral rami and the accessory nerve are entirely sensory. The results of the degeneration experiments are obviously in entire agreement with the oscillographic studies.

These findings agree with those obtained in the cat and rabbit; that is, that the proprioceptive fibres to the accessory muscles arise in the upper cervical dorsal root ganglia (2, 3, and 4, in monkey) and pass peripherally over the respective spinal nerves to join the extracranial portion of the spinal accessory nerve before passing to the muscles. Furthermore, our stimulation experiments in the cat, rabbit and monkey show that the anastomotic branches of the upper cervical nerves with the spinal accessory are entirely sensory. In man, as in the monkey, there are extraspinal anastomoses between C.2, C.3. and C.4 and the accessory nerve and it would therefore appear to be a reasonable conclusion that these branches contain sensory fibres destined for the sternocleidomastoid and trapezius muscles.

In the monkey, C.2 ventral ramus gives off a small branch which passes rostrally with a similar branch from C.1 and joins the hypoglossal nerve. C.2 fibres may also pass with C.3 fibres directly to the hypoglossal nerve more peripherally or, as is more usual, anastomose with the ramus descendens to form the ansa hypoglossi. Section of the rostral branch from C.2 to the hypoglossal nerve results in degeneration of a bundle of medium-small sized myelinated fibres which pass peripherally with the hypoglossus to enter the descending ramus. However, a small number may be traced peripherally in the hypoglossus directly into the tongue musculature. These fibres form about 2 per cent. to 5 per cent. of the total myelinated variety in the peripheral portion of the hypoglossal nerve. Similarly, section of that portion of the ventral ramus of C.2 which joins with that of C.3 to form the ansa, also leads to a small amount of degeneration in the most distal portion of the hypoglossal nerve. This contribution is less in amount, however, than that which accompanies this nerve from the rostral branch of C.2. This agrees with our results on Rhesus monkeys in which the C.2 dorsal root ganglion was removed (Corbin, Lhamon and Petit, 1937), and indicates that the degenerating fibres found in the hypoglossal nerve after section of C.2 are probably sensory in function.

In the rabbit, removal of the dorsal root ganglion or section of the ventral ramus of C.1 results in degeneration of from 1 per cent. to 5 per cent. of the myelinated fibres in the most peripheral portion of the hypoglossal nerve (Yee, Harrison and Corbin). Since the monkey rarely has a first cervical dorsal root ganglion (Hartman and Strauss, 1933; Corbin, Lhamon and Petit), the second cervical dorsal root ganglion evidently supplies muscle sense fibres to the tongue muscles of the monkey. However, it is difficult to explain our inability to demonstrate such a contribution in the cat (Hinsey and Corbin, 1934; Corbin and Harrison, 1938). Carleton's work on man, in which there was a loss of sense of position in the tongue following anæsthetization of the lingual mucosa, indicates that intramuscular postural sense in the tongue is very meagre, and might be entirely accounted for in the monkey and rabbit by the small number of fibres from the upper cervical dorsal root ganglia which course peripherally with the hypoglossal nerve.

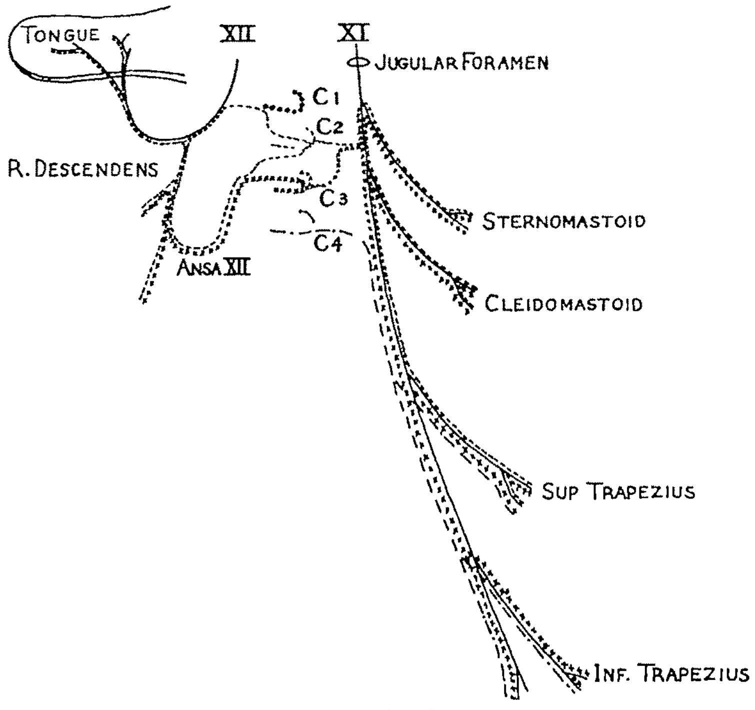

Diagram representing the sensory contribution of the upper cervical spinal nerves to the spinal accessory and hypoglossal nerves in the monkey (*Macacus rhesus*).

SUMMARY AND CONCLUSIONS.

Degeneration and oscillographic studies were made on fourteen Macacus rhesus monkeys in order to determine the course of proprioceptive fibres from the accessory musculature.

Stimulation experiments indicate that the anastomotic branches between the upper cervical ventral rami and the accessory nerve carry sensory fibres only. The ventral ramus of C.2 supplies postural sensibility primarily to the sternocleidomastoid muscles and to a lesser extent to the trapezii. The ventral ramus of C.3 also supplies the sternocleidomastoid muscles and contributes a considerable number to both trapezii. The ventral ramus of C.4. however, contributes sensory fibres to the trapezius group only.

As a result of these experiments and previous work on the cat and rabbit we conclude that the accessory musculature (sternomastoid, cleidomastoid and trapezii) is supplied with proprioceptive fibres, the cells of origin of which are situated in the dorsal root ganglia. These fibres pass peripherally over the respective cervical ventral rami finally anastomosing with the accessory nerve before entering the accessory muscles. It seems reasonable to conclude that a similar condition obtains in man.

Section of the ventral ramus of C.2 uniformly resulted in the degeneration of from 2 per cent. to 5 per cent. of the medium-small sized myelinated fibres in the most peripheral portion of the hypoglossal nerve. Since similar degeneration has been obtained following removal of dorsal root ganglion of C.2 in the monkey and of C.1 in the rabbit, we conclude that the degenerating fibres are sensory and proprioceptive to the tongue musculature.

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THE IDENTITY OF MYOTONIA CONGENITA (THOMSEN'S DISEASE), DYSTROPHIA MYOTONICA (MYOTONIA ATROPHICA) AND PARAMYOTONIA.

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SUMMARY.

(1) Introduction.
(2) The distribution of myotonia in myotonia congenita and dystrophia myotonica
(3) Pseudohypertrophy.
(4) Muscular atrophy.
(5) Weakness of muscles and abolished or diminished tendon reflexes.
(6) Autonomic Nervous System.
(7) Cataract.
(8) Mental Symptoms.
(9) Metabolism.
(10) Histopathology.
(11) Electrical Examination.
(12) Familial Incidence.
(13) Age of Onset and Age when Examined.
(14) Course.
(15) Heredity.
(16) Paramyotonia.
(17) Other Conditions in which Myotonia occurs.
(18) Conclusion.
Appendix.

(1) INTRODUCTION.

IN 1874 Leyden reported a case presenting myotonic symptoms, but interest in and study of myotonia congenita dates from the publication of Thomsen's paper in 1876.

It is possible that Leyden's case was one of dystrophia myotonica, since according to Guttmann (1891) his speech was slow ("langsam und unbeholfen"), a familiar feature of this malady.

Following the appearance of Erb's monograph on Thomsen's Disease (1886), in which the electrical reactions characteristic of myotonia were first described, cases combining muscular atrophy and myotonia began to be recorded, as for example by Jolly (1896), Hoffmann (1900), and Pelz (1907).

Rossolimo (1902) first suggested that cases presenting both myotonia and muscular atrophy should be regarded as a special variant of Thomsen's Disease.

Batten and Gibb (1909) reported a series of such cases and maintained that they were distinct from Thomsen's Disease, but Steinert (1909) believed that cases presenting atrophy started as typical cases of Thomsen's disease and did not belong to a separate category.

Since this date views have varied. Thus, Adie and Greenfield (1923), Curschmann (1906, 1912, 1915, 1925, 1936), Hauptmann (1916, 1919), Hirschfeld (1911), Nissen (1923), Curtius (1935), and Nevin (1938) have all regarded the two affections as distinct. On the other hand, their identity has been maintained by Noguès and Sirol (1899), Higier (1916), Rosett (1922), Guillain, Bertrand and Rouquès (1932), Massion and Vermiory V. (1936), O. Maas (1933) and Kramer and Quadfasel (1933). The question as to whether myotonia congenita, dystrophia myotonica and paramyotonia are to be regarded as a single, or as distinct, diseases is not a purely academic one, nor one of simple terminology.

If they represent no more than different stages of a single process then the hereditary factors must be the same in each case: that is, both pathology and heredity must be identical.

Clinically it is recognized that in the case of a malady believed to show heritable qualities, there may be clinical variations from family to family affected, yet we do not on this account believe that distinct diseases are in question. In myopathy, for example, the affected members of a single family may all show deviations of the same order from type, as in the topography of the wasting, the presence or absence of pseudohypertrophy and the rate of progress of the disease. Again in Huntington's chorea, age incidence and the relative predominance of chorea and of dementia may vary from family to family (Davenport and Müncey, 1916).

On the other hand, clinical similarity does not necessarily imply complete identity, since factors of heredity may vary.

Thus, there are recessive and dominant modes of inheritance in Friedreich's ataxy, and in the latter case the disease appears later and runs a more benign course. Bell, J. (1935) has shown that maladies with clinical resemblances may have different inheritance factors. In short, it appears that the various types of hereditary ataxy are inherited according to different Mendelian laws.

(2) THE DISTRIBUTION OF MYOTONIA IN MYOTONIA CONGENITA AND IN DYSTROPHIA MYOTONICA.

It has been maintained that while in myotonia congenita (Thomsen's disease) myotonia may be present in most of the striated musculature; in dystrophia myotonica it is essentially restricted to the tongue and thenar muscles.

In our experience, however, the myotonia in the latter disease may be present in almost every muscle of face, trunk and limbs. This conclusion was reached by Adie and Greenfield who say " while it is true that active myotonia is most obvious both to the patient and to the superficial observer in the hand grasps, we feel sure that a careful consideration of all the symptoms and the application of appropriate tests will disclose the fact that it is of much wider distribution in a large proportion of cases."

It is known that in dystrophia myotonica the myotonia disappears in the later stages of the illness in markedly wasted muscles, but the examination of a series of cases in an affected family, where the disease may be observed at different stages of development, shows that myotonia differs in degree and incidence in the different subjects.

(3) PSEUDOHYPERTROPHY.

Pseudohypertrophy has been observed both in myotonia congenita and in dystrophia myotonica. We have ourselves seen it in trunk and limb muscles in many cases. Case 1 in the Appendix is an example. We have also in a case of dystrophia myotonica seen the combination of muscular wasting with hypertrophy of thenar and hypothenar muscles. Probably the comparatively rare observation of pseudohypertrophy in dystrophia myotonica is due to its early appearance and to its disappearance before wasting occurs.

(4) MUSCULAR ATROPHY.

In the differentiation of dystrophia myotonica from Thomsen's disease, the presence of muscular wasting in the former has been regarded as of diagnostic importance (Steinert, 1909, Curschmann, 1906, Hauptmann, 1916), the facial muscles, sternomastoids, supinators and small hand muscles being characteristically affected in this way. Adie and Greenfield (1923), with whose observations our own agree, concluded that there was no characteristic topography of wasting. We have noted wasting in almost all the striated muscles, and also sparing of the sternomastoids, supinators and hand muscles.

Dr. Riddoch, in a private communication, has given us notes of a case in which he found normal sternomastoids, weakness and wasting of the flexors of wrist and fingers, of supinators, wrist extensors and facial muscles, with myotonia of hands and of orbicularis palpebrarum.

Although in the very numerous cases we have observed we have seen none without some sign of muscular wasting we consider it possible that such may occur. Again, weakness may be observed in certain muscles without unequivocal wasting, and in these the diagnosis of dystrophia myotonica is confirmed by the associated presence of such signs as diminished sexual power, baldness, lack of facial expression, early loss of teeth, or incipient cataract or mental abnormality.

Cases (1, 2, 3, 4) illustrating these points are briefly resuméd in the Appendix.

(5) Weakness of Muscles and Abolition or Diminution of Tendon-Jerks.

Although in his original paper Thomsen referred to neither of these abnormalities, Erb (1886) recorded them in his monograph on Thomsen's disease. Writing in Bumke's Handbuch (1936), Curschmann refers to the diminished frequency with which Thomsen's disease is now diagnosed and cites Sanders' paper (1935) in this connection. It seems that the reason for this is that more exhaustive clinical examination now reveals the signs that we have come to associate with dystrophia myotonica in cases of the kind in which they were formerly missed. A family recorded by Sanders as showing Thomsen's disease is of importance in this connection. It had been earlier recorded by van der Stok (1893) and by Delprat (1892). The last named noticed a defect of speech which is described as "sehr wenig accentuiert": a feature commonly noted in early cases of dystrophia myotonica. Sanders' own description of this family is incomplete, though he mentions the remarkable muscular weakness presented by some of its members.

Hirschfeld (1925) observed in the niece of a typical case of dystrophia myotonica evidences of myotonia only, but ten years later Curtius (1935) saw her and observed abolition of the ankle jerks and diagnosed her as having early dystrophia myotonica. Erb (1889) quoted Uibeleisen (1887) as having noted diminished tendon jerks in a case of Thomsen's disease.

(6) Autonomic Nervous System.

Autonomic imbalance is frequently in evidence in dystrophia myotonica. Case 2 in the Appendix showed myotonia, minimal signs of wasting and weakness, but marked hyperhydrosis. In his first case of

Thomsen's disease Erb reported a marble-like appearance of the skin, and Nissen (1923) found unilateral sweating in a typical case of Thomsen's disease (his own brother). No differentiation between the two maladies is possible, therefore, on this ground.

(7) CATARACT.

As is well known cataract is a frequent sign in dystrophia myotonica, but slit-lamp examination was unknown when Thomsen reported his cases, and Sanders does not report that he used this method of examination. Knaur's (1936) cases of supposed Thomsen's disease without wasting showed cataract in two instances. We have examined several cases of dystrophia myotonica in which an ophthalmologist failed to find cataract.

(8) MENTAL SYMPTOMS.

These are very common in both diseases. Many members of Thomsen's own family were affected, some of them seriously, while in the family examined by Sanders several members with no myotonic symptoms were mentally disordered. In neither family was any detailed psychiatric examination made, but if this had been done, no doubt the neurotic and psychotic symptoms would have corresponded to those described by us (1937) in members of families affected by dystrophia myotonica. There is, in fact, no evidence that the mental symptoms are different in the two diseases.

(9) METABOLISM.

Poucher and Woodward (1936) and Nevin (1938) have found differences in metabolism in the two diseases. In Thomsen's disease no creatine was found in the urine, there was increased tolerance for creatine, and the creatinine content of the urine was a high normal. Nevin suggested that this occurred because muscular hypertrophy caused a greater ability to store creatine and to convert it into creatinine, the natural end-product of muscle metabolism.

In dystrophia myotonica metabolism was the same as in cases of myopathy, namely decreased excretion of creatinine, while there was an excretion of creatine.

These observations, however, do not really point to any essential difference between Thomsen's disease and dystrophia myotonica. It is quite feasible that a muscle not affected by wasting. like a normal muscle, may have a normal creatinine metabolism, whereas the pathological metabolism in which creatine is excreted is naturally observed only when there is considerable wasting of muscle.

(10) Histopathology.

Slauck (1936) maintained that the histological pictures of dystrophia myotonica and myopathy were identical. It is obvious then that muscles affected by gross wasting in dystrophia myotonica differ entirely from muscles in a case of Thomsen's disease. No one, as far as we know, has detected any difference between the muscles in Thomsen's disease and those muscles in dystrophia myotonica which show no wasting or weakness.

(11) Electrical Examination.

Eichler and von Hattingberg (1938) have described differences in the behaviour of an active current in the two diseases. We do not doubt that such a difference was found, but this difference was presumably only the difference one would expect to find in a wasted muscle compared to one which was not wasted. These observations, therefore, have no value in distinguishing the two diseases as separate entities.

(12) Familial Incidence.

As already mentioned, Davenport has described different variants of Huntington's chorea, so that in one family mental symptoms predominate, while in others the principal symptoms are those of chorea.

The same principle probably applies in the case of dystrophia myotonica. In some families the myotonic signs tend to predominate, yet these families are not entirely free from other symptoms of dystrophia myotonica.

Some authors have maintained that no case of the one disease occurred in families in which the other was found. We are convinced, however, that this is not so. Boeters (1935) was also of this opinion.

As already pointed out, one member of Thomsen's own family undoubtedly was affected by dystrophia myotonica. We do not know if, in addition to the case examined by Schultze and Steinert, other members of this family were affected by muscle wasting. One of his own sons is described by Thomsen himself in a letter published by Seeligmüller (1879) in the following words, "This son had a slender and feeble physique ('gracilen und schmächtigen Körperbau'), but nevertheless a quite remarkable development of muscle, the like of which I have never seen, which is especially noticeable on the thighs."

Vewey and Legras (1933) reported a family, some of whose members suffered from dystrophia myotonica while others were affected by typical symptoms of Erb's myopathy.

These findings were similar to those obtained by us in one family, of which many members suffered from typical dystrophia myotonica, but in two boys, both idiots, neither Dr. R. G. Gordon nor one of us (A.S.P.) could find any trace of myotonia. The sterno-mastoids were particularly wasted.

A superficial examination of some of the family Jo (see No. 5 in Appendix) might have led to the belief that certain members were suffering from Thomsen's disease, and if reliance had been placed upon what the original patient had said, it might have been considered that a number of individuals had escaped altogether. Detailed examination, however, showed that practically all had definite signs of dystrophia myotonica. In other families as well, when a patient was found to have typical signs of dystrophia myotonica, we discovered that so-called healthy relatives, who were at work, were affected by definite signs of myotonia, while signs of wasting were very slight.

Isolated cases of dystrophia myotonica in a family have been described until quite recently. Such accounts are, we believe, of no value unless parents, brothers, sisters, children and cousins are examined by experts. We have examined numerous patients who reported that they had no relatives affected like them. When, however, we examined these relatives we found definite signs in them. Numerous individuals with definite signs of dystrophia myotonica maintained that they were perfectly healthy. We have, therefore, to take with reserve reports of isolated cases (we may add that, of course, the diagnosis of myotonia acquisita (Talma-Krabbe) has to be considered in such cases).

(13) Age of Onset and Age When Examined.

As its name implies, myotonia congenita has been supposed to be a congenital affection, while most authorities have described dystrophia myotonica as beginning between the ages of 30 and 40 years.

Examination of the literature, however, as well as our own observations, fails to substantiate any real difference in this respect.

Of the cases of myotonia congenita described by Erb in his monograph, the first two were affected in early infancy, while in the third case the first signs were found at the age of 16 years.

Erb describes in his monograph (1886) three cases who when examined were 14, 15 and 21 years, and he collected numerous cases published by other authors up to 1885. Nearly all these cases were in the early 'twenties when published.

This also holds for the cases published by van der Stok (1893).

In his later article Erb mentioned the age of patients suffering from

Thomsen's disease whose cases had been published by other authors as follows:—

Danillo	24	years
T. Buzzard	16 and 20	„
Uibeleisen	20	„
Jacoby	24	„
Banham	18	„
Blumenau	30	„
Nearonow	23	„
Wising	19	„
Martius and Hansemann	21	„
Renner	17 and 23	„

Some cases which Erb has observed since his monograph was published, were aged 19, 26, 26, 31 and 34 years.

Among these cases some were affected by signs of dystrophia myotonica, as Curschmann has stated (1936).

In many cases in the literature of Thomsen's disease, the age of onset has not been reported.

The belief that the two conditions are distinct rests, therefore, apparently on the fact that myotonica congenita has often been diagnosed in patients who were young, and that those cases have not been followed up.

Again, on the other hand, dystrophia myotonica has sometimes been observed by us as occurring in early infancy. This was pointed out by one of us (O.M.) (1937, pp. 508 and 509) and many cases of dystrophia myotonica reported in this paper showed their first symptoms at any early age.

(14) COURSE.

There has been a limited number of cases of myotonia congenita, which, on being examined again after an interval of some years have shown definite signs of dystrophia myotonica. Such cases are of great importance in supporting the view that the two conditions are in fact identical. Case 1, for instance (see Appendix), was published by Ironside in 1926 as a case of Thomsen's disease. Although at the present time wasting is not so striking a feature as the myotonia, yet it is sufficient to put the diagnosis beyond doubt, especially as other symptoms (hyperhidrosis and diminished sexual power) are taken into consideration.

Hitzenberger (1920) published a case in which the disease started at the age of 23, and was six years later diagnosed as Thomsen's disease. Nevertheless at the age of 38, the man showed indisputable symptoms of dystrophia myotonica.

A case of Steinert (1910) was a typical case of Thomsen's disease for many years, but atrophy of the testicles ensued at the age of 45.

Kolb, Harvey and Whitehill (1938) reported the following case: A boy began to suffer from myotonic symptoms at the age of 8 years. He was demonstrated by another author as a case of Thomsen's disease when aged 14. It would appear that nothing suggesting dystrophia myotonica was detected at the time. Kolb and his co-workers examined him at the age of 33. They found myotonia only in his thenars, with no hypertrophy or atrophy of muscles, but early baldness and high palate. A slit-lamp examination could not be made.

The diagnosis was dystrophia myotonica sine atrophia.

Curschmann (1936) maintained that there was a marked difference between the two diseases, as dystrophia myotonica was always characterized by cachexia at a later stage (p. 441), while myotonia congenita took one of three courses: it remained at a standstill, was remittent or was slowly progressive (pp. 446 and 464).

We have, however, examined numerous cases with definite symptoms of dystrophia myotonica, some over 50 and up to 70 years of age, who were in no degree cachectic.

On the other hand certain cases of Thomsen's disease in the literature show a general progressive physical deterioration.

The grandfather of Dr. Thomsen himself, who in his youth was a page at the Danish Court, a post that presupposes a reasonably good physique, had later to give up a military career because of his state of decrepitude.

(15) HEREDITY.

Thomsen, Nissen and Sanders have described how myotonia congenita has occurred in subsequent generations of a family. One of us (O.M.) has shown, as other authors had previously, that the same holds for dystrophia myotonica (1937, p. 514). It would be out of place here to discuss the form which the heredity takes. It is enough to point out that there is no difference between the two disorders with regard to the mode of transmission.

(16) PARAMYOTONIA.

Cases published by Eulenburg (1886) as well as by Martius and Hansemann (1889) in which myotonia occurred only in cold weather, were given the name of "paramyotonia," and regarded by various writers as constituting a different entity from myotonia congenita. Curschmann (1936, p. 462) discussed these cases and maintained their close relationship to, if not identity with, myotonia congenita. on the ground that such cases were found in families affected by Thomsen's disease. Nevertheless later on in the same article (p. 484) he stated that it was probable that this rare condition paramyotonia congenita was an independent disease (Selbständige Krankheit).

The fact that most cases in which myotonic symptoms occur are more markedly affected in cold weather and freer from inconvenience in warm weather makes it probable that so-called "paramyotonia" is only a slight variant.

In this connection the following case is of interest, which we examined some years ago.

E M., a male, aged 35. A cousin was described by O. Maas and H. Zondek (1920) as a typical case of dystrophia myotonica. E. M. worked as a farmer. Thyroid a little enlarged. He had a haggard look. Face was thin, blowing out cheeks was weak, sterno-mastoids as well as all the muscles in the right upper limb and in both lower limbs were normal, but all the muscles in the left forearm as well as the left thenar muscles were wasted. Myotonia was not observed in any muscle on examination, but he reported typical myotonic stiffness in his hands in cold and wet weather.

This case shows that the symptom "paramyotonia" may occur in families affected by dystrophia myotonica.

Similar cases have been reported by Schott (1935). They suffered from intermittent myotonic symptoms and wasting in the small muscles of the hands. Schott named the malady "Paramyotonia congenita."

(17) Other Conditions in Which Myotonia May Occur.

There are two groups of cases which may give rise to the wrong diagnosis of myotonia congenita.

Cases have been described by Hoffmann and by Kramer (1918) in which the symptoms of myotonia evidently resulted from thyroid malfunction. Other cases of this type have recently been reported by Nevin (1938).

A typical case was observed at the National Hospital in 1934.

S. McL., a female, aged 20 (Case of Dr. Martin). There was myotonia, and some muscles appeared hypertrophied. After treatment with thyroid extract, myotonia and hypertrophy disappeared.

The other group of cases in which myotonic symptoms occur have been described by Talma (1892) and has recently been discussed fully by Krabbe (1934). In these cases myotonia, and also muscle hypertrophy, came on after an infectious disease, probably always in combination with polyneuritis. A case which we considered as belonging to this group was an in-patient at the National Hospital under the late Dr. Adie in 1926.

W. W., a male, aged 62. He had complained two years previously of pins and needles which later developed into stiffness. On examination typical myotonia was observed in all the limbs. There was no wasting Alterations in his lenses were found, but these were different from the type which occur in dystrophia myotonica (see Adie and Ironside, 1925).

In our view the acute onset of myotonia, as well as the age at which the disturbance started, are strongly against the diagnosis of "myotonia congenita." We agree with Krabbe's opinion that such cases are true "myotonia acquisita," *which is in no respect related to "Thomsen's disease."*

On the other hand, however, not all cases published as coming under this diagnosis do in fact belong to the type described by Krabbe. A case demonstrated by Jolly, for instance (1896) is undoubtedly one of dystrophia myotonica, for a son of that patient has been described by one of us (Bielschowsky, Maas, Ostertag, 1933) as a typical case of that disease. Also one of Talma's cases is very doubtful as no infectious disease preceded the myotonia.

Myotonia was further described by Schlesinger (1902) as a rare symptom in cases of syringomyelia. We think it likely that those cases were similar to the case published by Maas and Critchley (1934-35) in which dystrophia myotonica was combined with syringomyelia.

Lastly, we would mention an interesting observation made by Worster-Drought (1932) who described a family affected by an obscure hereditary nervous disease. One member was affected by myotonia of upper and lower limbs in addition to other organic signs in the central nervous system. It would appear improbable that this was a case of dystrophia myotonica.

We cannot, therefore, deny that the symptom of myotonia may occur in a familial disease of the nervous system other than dystrophia myotonica.

(18) Conclusion.

We have traced the conception of the syndrome myotonia congenita or Thomsen's disease in the literature. We have examined in detail those characteristics in virtue of which some writers have sought to distinguish it from dystrophia myotonica. All the evidence goes to show that so-called myotonia congenita is merely an early stage of dystrophia myotonica. Nearly all the cases of myotonia congenita described in the literature have been between the ages of 17 and 30. Almost no case has been watched over a number of years. In certain cases where this has been done, signs of dystrophia myotonica have been found to develop. In recent years, as remarked by Curschmann, myotonia congenita has been very rarely diagnosed. This is evidently because neurologists are on the look-out in a case of myotonia for slight wasting, for cataract as revealed by slit-lamp examination, for atrophy of the testicles and other symptoms both in the patient himself and in the members of his family. Where these occur myotonia congenita is not diagnosed. Yet a generation ago, when these symptoms were not looked for, myotonia congenita was more frequently diagnosed.

We have attempted to show that none of the arguments are really valid which have led to the separation of the two diseases myotonia congenita and dystrophia myotonica. These are based on the alleged difference of distribution of the myotonia and the wasting throughout the body; the presence of pseudo-hypertrophy, absence of certain reflexes, mental symptoms and the rest.

The only sense in which myotonia congenita can be said to exist is that in certain families there is a tendency for the myotonia to be prominent and for the wasting and other symptoms to be less pronounced and to come on at a later date. Nevertheless such families are more truly said to exhibit a variant of dystrophia myotonica than a separate disease.

Similarly, if a patient is found to be suffering from paramyotonia, that is myotonia which may occur in cold weather, we suggest that a complete examination of his relatives will reveal some members who show symptoms of dystrophia myotonica. The symptom-complex described by Talma and Krabbe as " Acquired Myotonia " is, however, quite a different disease from dystrophia myotonica, which is a hereditary condition.

We hope, therefore, that we have proved beyond reasonable doubt that myotonia congenita, dystrophia myotonica and paramyotonia are essentially one and the same disease. We consider that it would be logical to widen the conception of Thomsen's disease to cover all the symptoms included under the other two names. The two latter names might be abandoned, thus allowing *the whole disorder to be known as Thomsen's disease or myotonia congenita.*

In conclusion we would express our thanks to the members of the honorary staff of the National Hospital and of other hospitals for their assistance in providing material and also to Mr. C. Goulden and Mr. T. C. Summers of the London Hospital for the examination of numerous cases with regard to cataract, and to Dr. L. D. Bailey for the electrical examination of our cases.

We are both also indebted to the Medical Research Council for grants in connection with this work.

APPENDIX.

Case 1.

J. C. G., aged 34 (case of Dr. Brinton). Complained of stiffness in all his limbs and in moving his eyes, since infancy. When questioned he said that his face had definitely become thinner during the last two or three years. On examination, there was hypertrophy of some of the muscles of the upper and lower limbs, especially the deltoids, biceps brachii, muscles of the forearms, quadriceps and muscles of the calves. There was slight, but definite wasting of the temporal and facial muscles, sterno-mastoids, peroneal muscles. There was slight weakness of his buccinators and also in his grip. There was slight but definite weakness in dorsal flexion of the feet and of the toes. The left triceps jerk was absent or only showed a flicker. There was typical myotonia in the tongue, thenars, hypothenars, extensors and flexors of the forearms. There was also some hyperhidrosis and diminished sexual power. His memory had deteriorated in the last three years and his general interest in life had waned.

Case 2.

X. Y., a male, aged 26. His father aged 61, healthy, able to do very hard physical work, but suffered from stiffness in his arms for some decades. The description of the stiffness was quite typical, and he became bald at an early age. He was not examined by us.

X. Y., an only child, feels perfectly healthy, is exceptionally intelligent and is engaged in scientific work. The stiffness in the arms and legs has been present for many years, he thinks since infancy. He did not, however, pay much attention to this. He complained of double vision and squint if he moved his eyes quickly. He sweats readily and tires more quickly than most people, e.g. when swimming. His hair receded from his forehead as early as the age of 14 years. On examination mechanical myotonia was seen in his tongue in quite a marked degree The strength of the buccinators was slightly diminished. There was a slight myotonic response on tapping the thenars, hypothenars, flexors and extensors of the forearms. Dorsal flexion of the left foot was not very strong. Slight myotonic facies.

He said that many members of his family had suffered from very early loss of their teeth and also from early baldness. All the children of one of his father's sisters had lost all their teeth before the age of 21. The youngest sister of his father had died at the age of 12. She was mentally disordered. The youngest daughter of another sister of his father went to a special school for mental defectives. Several of his cousins suffered from cramps.

Case 3.—(A case of Dr D. Brinton).

A. Bo., aged 31, complained of general weakness since infancy. He was operated on for cataract at the age of 31. General stiffness in slight degree since infancy.

Slight wasting of facial muscles.

Definite wasting of sterno-mastoids

Forearms poor, but no special wasting of supinators, hand muscles not wasted.

Weakness of facial muscles, both grips, dorsal flexion of the feet.

Mechanical myotonia in thenars, hypothenars, extensors and flexors of the forearms.

The other members of his family examined were his father, his father's sister, his own brother and three sisters All these showed signs of dystrophia myotonica.

Case 4.—(A case of Dr. S. K. Westmann).

Mrs. G., aged 30. The brief report on her family gave no reason for supposing that other members of her family were affected by myotonia. Mrs. G. had suffered from intermittent stiffness in her upper and lower limbs for ten years. This stiffness would disappear for weeks and at times for months, but became more evident after she became pregnant in February, 1938.

On examination, slight but typical myotonia was found in many muscles of upper and lower limbs. It was much more conspicuous at the second examination carried out 14 days after the first one (in June, 1938).

A doubtful wasting was found in her temporals. Although right handed, her right fore-arm was a little smaller than the left. The right supinator longus was a little smaller and weaker than the left, as confirmed by Dr. Riddoch. She reported also that she sometimes suffered from fingers which would go quite white and dead.

No other abnormality was found

Case 5.—(A case of Dr. A. W. Spence).

J. J. A female, aged 44. She was healthy till the age of 38, when she showed marked signs of dystrophia myotonica, although the supinators are still good ! One maternal aunt had cataract.

Five sisters and two brothers of this woman were examined as well as nine siblings in the next generation, all of whom were affected with more or less marked signs of dystrophia myotonica, and yet none were incapacitated.

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CLINICAL INVESTIGATION OF OLFACTORY FUNCTION IN BRAIN TUMOUR PATIENTS.

BY JOHN D. SPILLANE.[1]

RECENT electro-physiological studies on the sense of smell in animals (Hasama, 1934, Adrian and Ludwig, 1938) have prompted the publication of this paper, which deals with the application of the new methods of quantitative olfactometry, as devised by Elsberg and his associates (1935), in clinical neurology. Elsberg's studies arose out of a desire to improve the early diagnosis of olfactory groove meningiomas and progressed to an investigation of alterations of olfactory function in tumours arising in the substance of the cerebral hemispheres. A large number of cerebral tumours have now been investigated (Elsberg, Levy and Brewer, 1935 and 1936) and a summary of their findings has recently been published (Elsberg and Stewart, 1938).

The claims are striking and have been the subject of much comment in American neurological circles. Up till the present time, however (October, 1938), there have been no similar studies reported by other workers, except those of Adler and Finley (1938) who recorded their results in a series of brain tumours.

There is thus no need for an apology for this paper, which is based on an independent study of the method in 140 individuals, normal and diseased, carried out at Cardiff and in Dr. Elsberg's laboratories at the Neurological Institute of New York.

THE PRINCIPLE OF THE TESTS.

An odour cannot be appreciated if the breath is held. Before it can be appreciated and identified a sufficient quantity of that odour must impinge upon the olfactory membrane with a certain degree of force. There must, therefore, exist a level of threshold stimulation at which the odour is first detected. Now, as pointed out by Elsberg, all previous tests of olfactory function have entailed sniffing of odorous substances by the individual being tested, so that accurate quantitative measurements have been impossible. It is difficult to measure the degree and force of sniffing.

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The new tests were devised to exclude this variable factor ; a known volume of odour was *injected* into the nostrils *during a period of voluntary apnœa,* so that the level of threshold recognition could be ascertained.

THE APPARATUS AND PROCEDURE.

A full description of the technique will not be furnished here, only the essentials will be enumerated. The apparatus consists of a standard test bottle, with inlet and outlet tubes, containing a known volume of odorous substance (coffee or citral), a glass syringe and a set of nose-pieces. Two tests are made ; the blast injection test and the stream injection test.

The blast injection test.—A known volume of air is injected into the test bottle and released into one nostril, through the nose-piece attached to the outlet tube, during a period of voluntary apnœa. The number of c.c. of odour that must be released into one nostril in order that the odour be identified is termed the minimum identifiable odour (M.I.O.). Be it noted. that the volume of odour released from the test bottle must necessarily equal the volume of air previously injected into the test bottle from the syringe.

The stream injection test.—This procedure is used for the study of olfactory fatigue. A stream of air, of known volume-rate, is passed from a tank of compressed air through the test bottle and thence to the nostril, for a period of thirty seconds. The patient is instructed to breath quietly through the mouth. Blast injections of the previously determined M.I.O. are then made at thirty-second intervals and the time that elapses before the odour is again identified, is measured. This is the duration of olfactory fatigue.

The two tests are performed in both nostrils and with the two substances, coffee and citral. Thus, the M.I.O. and the duration of olfactory fatigue are determined for coffee and citral in each nostril. The procedure, although relatively simple of execution, with practice, requires considerable attention to detail if results are to be reliable. The whole test can be completed in about one hour if the patient is co-operative. Frequently, however, it is advisable that the patient be subjected to testing with only one substance at the first interview.

THE RESULTS.

We shall first consider the normal findings and then proceed to a discussion of those obtained in cerebral tumour patients.

A study of forty normal individuals led Elsberg to assert that the M.I.O. for coffee and citral were 8—10 c.c. and 6—8 c.c. respectively, while the duration of olfactory fatigue varied between 1·5 and 2·5 minutes for coffee, and 2·5 and 3·5 minutes for citral. Adler and Finley (1938) reported that they frequently observed the M.I.O. to be lower than the above figures, namely, 3 to 4 c.c. for coffee and citral, but that in no instance was it higher than Elsberg's figures. They do not mention the number of their controls.

In the present series of 140 observations there were 60 normal controls, mostly medical students. Although the majority, 41, or 66 per cent., were discovered to have M.I.O.s confirming Elsberg's figures, it became amply evident that there were plenty of individuals whose olfactory acuity was of a lower level. The findings of Adler and Finley were also corroborated.

TABLE I.

Minimum identifiable odour (M.I.O.) in 60 normal controls.

	Number	
M.I.O.	Coffee	Citral
1— 3 c.c.	0	6
3— 6 „	10	4
6—10 „	41	41
10—15 „	9	7
15—20 „	0	2
20—30 „	0	0

In this control group, needless to say, care was taken to exclude local nasal conditions that would lessen olfactory acuity. All individuals were first subjected to a Zwaardemaker test.

Olfactory fatigue studies were made on only thirty of the above control group, but even in this small series marked variations were found and it was concluded that the duration of normal olfactory fatigue in this test ranged from ½ to 4½ minutes. Here again, the majority, 23, or 80 per cent., gave figures in accordance with Elsberg's findings. (Table II.)

TABLE II.

Olfactory fatigue in thirty normal controls

	Number	
Olfactory Fatigue	Coffee	Citral
½—1 min.	1	0
1—2 min.	3	4
2—3 min.	24	22
3—4 min.	2	2
4—5 min.	0	2

RESULTS IN BRAIN TUMOURS.

Elsberg's observations have led him to conclude that pressure on one olfactory nerve, as by olfactory groove meningiomas, suprasellar meningiomas, pituitary tumours that have extended beyond the confines of the sella turcica and aneurysms of the internal carotid artery, leads to a raised M.I.O. on that side. If both olfactory nerves are pressed upon, the M.I.O. of both sides is higher than normal, the greatest increase being found on the side most affected.

In supratentorial intracerebral neoplasms and in large dural growths buried in the brain, the M.I.O. is not raised but the duration of fatigue is prolonged on the same side as that of the neoplasm.

In frontal lobe tumours that extend to the undersurface of one lobe so that the olfactory bulb or tracts are subjected to direct pressure, the M.I.O. on the affected side is larger than normal *and* the duration of olfactory fatigue is prolonged.

Elsberg also added that many degenerative and inflammatory conditions of the brain could provide similar olfactory patterns.

In this investigation 80 consecutive suspect brain tumour patients were studied. At the outset, it should be realized that Elsberg has repeatedly stressed the fact that the value of the tests lies not so much in diagnosis as in localization of brain tumours. However, as precisely similar olfactory patterns may be obtained in other organic brain diseases, it should be remembered that in the interpretation of results, the dice will be heavily loaded in his favour if the observer merely publishes those cases in which a brain tumour was subsequently found to exist. And surely, if the diagnosis of tumour has already been made and localization decided, before olfactory tests are made, then there is little practical value in the method whether the tests succeed or fail in localization. The only criterion of the actual value of the tests would be the percentage successful localizations in previously diagnosed, but unlocalized, brain tumours. It is this point which has been continually ignored in all published reports.

In the latest report (Elsberg and Stewart, 1938) the claim is made for 74 per cent. correct localization in 101 supratentorial tumours ; no localization in 22·9 per cent. and incorrect localization in 2·9 per cent. In 81 per cent. of 150 patients who eventually proved to have no tumour, the olfactory tests gave no evidence of a localized lesion. Such claims, if confirmed, would confer on quantitative olfactometry a degree of exactness and usefulness in clinical neurology, which would compare very favourably with that obtained in ventriculography and encephalography. A hitherto neglected cranial nerve would, in the future, deserve the same attention of the clinician that he now devotes to the optic fundus exclusively. That such will not be the case seems indicated from the results of this study.

In Table III are outlined the values of the M.I.O. and the duration of olfactory fatigue in 35 brain tumours. In only 11 instances was localization effected by the olfactory tests; in two additional cases the tumour was lateralized to the correct hemisphere, but to the wrong lobe. Localization was incorrect in 7 instances, while no information was obtained in the remaining 15 cases. In the latter group, however, were two internal carotid artery aneurysms, one cerebellar tumour and four pituitary tumours which had not extended beyond the sella turcica.

Of three subfrontal meningiomas two were localized; no information was obtained in the third.

Of eleven frontal tumours four were correctly localized; localization was incorrect in two while in the remaining five cases no information was obtained.

Among seven pituitary tumours there were two in which reduction of olfactory acuity suggested that the tumour had extended beyond the sella turcica. This was confirmed in both cases by operation. In one of them, Case 3, marked progression of the lesion, under X-ray therapy, with rapid reduction in visual fields was found to be accompanied by corresponding elevation of the minimum identifiable odour for both nostrils.

The above 35 cases were the proven brain tumour patients in a series of 80 consecutive brain tumour suspects. In the remaining 45 individuals, epileptics, psychotics, arteriosclerotics, etc., no instance of an olfactory pattern was encountered which pointed to a local brain lesion. In many, however, there was considerable diminution of function of the olfactory brain. As a control group they also served to indicate that there exist wider values for the M.I.O. and the duration of olfactory fatigue than those laid down by Elsberg.

DISCUSSION.

In attempting to account for the discrepancy between the above findings and those of Elsberg a few theoretical considerations might prove helpful and instructive. Phylogenetically old, the rhinencephalon in man can play but little part in establishing contacts with his environments and marked variation in reaction to olfactory stimuli would naturally be expected in different individuals. In relatively few is the olfactory sense highly developed; in a correspondingly large group minor differences would hence be of little significance.

Histological studies of recent years (Cajal, 1911 and Winkler, 1918) have indicated the existence of connections between the two sides of the rhinencephalon. Olfactory nerve fibres crossing in the anterior commissure have been repeatedly demonstrated. Hence, it might be expected that unilateral olfactory disturbances might be compensated by activity of the opposite side. That such does actually happen is suggested by

Elsberg's demonstration that overstimulation of one olfactory membrane can result in reduction of contralateral olfactory acuity. The recent observation of the author (Spillane, 1938) that a condition of "olfactory alloæsthesia" may arise in unilateral cerebral disease, strengthens this point of view. Under this title was described a condition found in unilateral cerebral tumours characterized by a tendency for a stimulus applied to the olfactory membrane on the tumour side to be appreciated as if it arose from the opposite side. Such indications of bilaterality of function and innervation would render the interpretation of unilateral disorders of olfactory function extremely hazardous. But, as Elsberg has remarked, while commenting on the conclusion of Henschen (1919) in a clinical-pathological study (that the olfactory centres are so completely innervated bilaterally that unilateral alteration of olfactory function rarely arises in unilateral disease), former tests of olfactory function have been too gross to detect finer disturbances.

A second approach in this study is gained from a consideration of the physiological processes involved in the recognition of an odour. With gradually increasing olfactory stimuli several stages in the recognition of an odour can be detected. The first sensation experienced is one of odour-perception, a threshold level. With increase in the strength of the stimulus comes the realization that the odour is familiar, but recognition is still lacking. Finally, the stimulus reaches a strength at which the odour is named (the minimum identifiable odour, M.I.O., of Elsberg). Now, in comparing the olfactory acuity of a group of individuals it must be realized that wide variations *in these three stages* exist, so that a true index of olfactory acuity may not be obtained if thresholds of *odour-recognition* are investigated. The threshold of *odour-perception* may be the same in many individuals, but varying ability in the naming of the odour concerned would lead to great differences in the thresholds of *odour-recognition* in those subjects. Similarly, individuals who name odours at a certain level of stimulation may actually possess vastly different abilities in odour perception. Hence, in studying the olfactory functions in any group of subjects, a truer index of comparison would be the thresholds for odour-perception rather than those of odour-recognition. The latter is not a true threshold stimulus as it involves previous experience and other mental factors.

From the practical standpoint the tests present several drawbacks. The most outstanding is that their success is too dependent on the co-operation of the patient. In trained individuals, such as formed the control material on which were based several of Elsberg's observations, the tests are relatively simple. In any large group of hospital patients, however, many will be encountered who prove utterly incapable of grasping the essentials of the manœuvres and on whom the tests cannot be completed. Moreover, from the very nature of their lesions many brain tumour suspects, are quite unable to offer the necessary degree of co-operation. In the present series, there were approximately a further twenty subjects with brain tumours on whom the tests could not be carried out. Adler and Finley experienced similar results.

In the determination of the duration of olfactory fatigue—that part of the procedure which proved to be of the least practical value—a fallacy becomes apparent which theoretically may be of some account. It is this. When the M.I.O. is first determined the identity of the odour is *unknown* to the subject. When the fatigue tests are made, however, the odour is *known* to the patient. Now, one has repeatedly demonstrated the fact that M.I.O.s before and after the identity of the odour is revealed are often entirely different. Before, the value may be 10 c.c., and afterwards, much less, 6 or 7 c.c. Elsberg himself has demonstrated that a reduction in the value of the M.I.O. can be obtained if the blast injection is made at a moment when the subject recalls that odour to his memory. Hence, the values obtained for the duration of olfactory fatigue cannot be regarded as a *quantitative* index of the refractory state of the olfactory apparatus at the time of examination.

SUMMARY AND CONCLUSIONS.

A study has been made of Elsberg's recently introduced method of quantitative olfactometry. 140 individuals were investigated; 60 normal controls, and 80 suspect brain tumour patients.

It was concluded that the new tests of olfactory function far excel those of former years in both accuracy and reliability. In addition, they are quantitative in nature, being based not upon the principle of sniffing of odorous substances, but upon that of the injection of known volumes of odour into the nostrils during periods of voluntary apnœa. By this method a study can be made of the threshold levels of odour-perception and odour-recognition (minimum identifiable odour or M.I.O.) for any odorous substance. A measure of the duration of the relative refractory period of the olfactory apparatus may also be obtained by studying the recovery-rate in odour-recognition following prolonged overstimulation of the olfactory membranes (duration of olfactory fatigue).

Values for the M.I.O. and duration of the olfactory fatigue in 60 normal individuals indicated that there is a wider range of variation than that indicated by Elsberg. Nevertheless, it was confirmed that the majority of individuals possess roughly similar degrees of olfactory acuity when gross local conditions of the nasal passages have been excluded.

TABLE III.—DATA IN THIRTY-FIVE CASES OF BRAIN TUMOUR.

	Minimum identifiable odour				Olfactory fatigue					
	Coffee		Citral		Coffee		Citral			
Case	Right	Left	Right	Left	Right	Left	Right	Left	Location	Confirmed diagnosis
1	18	22	80	80	10	16	—	—	Midline	Pineal tumour
2	9	10	4	5	6¼	1	1	1	—	Suprasellar meningioma
3	7	7	7	7	4½	8	2	4¼		Pituitary extrasellar
	11	11	8	11	9	6	8	10	Midline	
4	8	80	8	20	10	10	4	6½	Left	Left hemisphere
5	18	7	7	5	4½	½	1½	1½	—	Right internal carotid artery aneurysm
6	30	8	80	15	—	10	—	5½	Bilateral	Meningioma at base
7	18	8	16	4	10	10	7	2	Right frontal	Cerebellar
8	6	80	18	80	10	—	6½	—	Bilateral frontal	Left temporal
	9	80	22	27	10	—	2	7½		
9	6	7	8	4	1	8	4½	8½	—	Pituitary
10	25	80	15	80	4½	—	½	—	Subfrontal	Subfrontal meningioma
11	20	30	20	80	1½	—	10	—	Subfrontal	Subfrontal meningioma
12	4	4	4	6	1½	4½	1	1½	—	Right internal carotid artery aneurysm
	5	5	5	4	0	0	0	2¼	—	
13	8	80	5	9	2	—	1	10	Left frontal	Left occipital
14	8	7	8	7	8¼	10	1	8½	—	
	11	14	10	16	1	4	7	2¼	? frontal	Right frontal
15	7	9	7	7	10	8½	7¼	8	Right frontal	Pituitary extrasellar
16	4	5	4	5	0	1¼	1½	2	—	Right frontal
17	12	8	11	7	¼	0	0	½	Right extracerebral	Right intracerebral
	11	8	9	7	2	½	1½	1		
18	19	5	18	5	2	2½	1¼	0	Right subfrontal	Left frontal
19	5	8	5	8	1	1	0½	1½	—	
	10	7	8	5	4¼	2	5	2½	Right frontal	Left frontal
20	6	8	4	6	2	8½	2¼	0	—	Right frontal
21	6	7	8	8	2¼	2¼	1	4½	—	Left frontoparietal
	7	6	5	5	0	2½	7	1½	—	
22	8	9	8	6	2	2	1¼	0	—	Left frontal
23	11	10	6	5	2	6	1	1	—	Right cerebellar
24	5	7	4	4	0	0	2½	1¼	—	
	2	5	2	4	8½	2	1	8½	—	Pituitary
25	5	10	6	5	8	8½	1	8	—	Pituitary
26	80	80	18	80	—	—	1½	—	Subfrontal	Frontal meningioma
27	18	80	10	17	5	—	0	0	Subfrontal	Suprasellar glioma
28	25	15	28	18	8½	0	10	10	Right frontal midline	Right frontal
29	80	12	80	9	—	0	—	1½	Midline	Pituitary
30	12	0	9	8	2½	2	0	1	—	Pituitary
31	11	8	18	6	8½	0	6½	2	Right frontal	Right frontal
32	22	8	10	7	2½	8¼	1½	5	? Right subfrontal	Left cerebellar
33	18	80	29	80	7	8½	8½	—	Subfrontal	Left temporal
34	7	8	4	4	1½	8½	¼	2½	—	Subfrontal mainly left
35	6	10	3	7	¼	¼	½	8½	—	Right temporal

By this procedure further knowledge of olfactory functions may be gained. For instance, that olfactory fatigue is central rather than peripheral in origin, is suggested by the observation that the duration of olfactory fatigue is frequently prolonged in cerebral tumour patients on the side of the lesion.

The classification of odours may be studied by this method (Elsberg, 1935).

The practical application of the tests in clinical neurology is, however, limited, thus far, to the early detection of interference with the function of olfactory nerves and bulbs. Pressure by tumours, such as olfactory groove meningiomas, sphenoid ridge meningiomas and other neoplasms in the subfrontal region, lead to a raising of the M.I.O. on the side of the lesion. Such tumour pressure may thus be detected before complete anosmia has resulted, so that complete removal of the tumour may be attempted before it has attained large proportions.

Evidence is adduced that the tests may be of some value in indicating the spread of a pituitary neoplasm beyond the confines of the sella turcica. In such cases, raised M.I.O.s are evidence of pressure by the tumour upon extracerebral olfactory pathways. Intrasellar pituitary growths do not interfere with olfactory function.

Confirmation is lacking that the tests are of value in the localization of intracerebral growths. Of 11 frontal tumours only four were correctly localized by the presence of prolonged duration of olfactory fatigue, without change in the M.I.O., on the side of the tumour.

Finally, the high degree of sustained co-operation that is required of the patient further limits the practical application of the method in clinical neurology.

I wish to thank Dr. C. A. Elsberg for giving me the opportunity to make this investigation at the Neurological Institute of New York.

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NOTICES OF RECENT PUBLICATIONS.

Histological Technique for Intracranial Tumours. By DOROTHY S. RUSSELL. Oxford University Press. 1939. Pp. 71, with 6 illustrations. Price 7s. 6d.

It has long been recognized that more is needed for the histological diagnosis of intracranial tumours than paraffin sections stained with hæmatoxylin and eosin. But in spite of the increasing interest in intracranial tumours there are still too few laboratories, at least in this country, where any but the most routine staining methods are employed. Dr. Russell's little book should, therefore, be of great value. She does not pretend to include in it all the methods that have been or may be applied to the study of intracranial tumours. For that a more comprehensive text book such as the Microtomist's Vade-Mecum is needed. Rather she gives a full and practical description of the methods which she has found to be most useful. The book must, therefore, be judged by what it includes rather than from its omissions, and as a practical guide to well-tried methods of staining it deserves nothing but praise. The most obvious omission is that of the Gros Bielschowsky technique. This method has proved so valuable in correcting current theories as to the relationship of nerve fibres to the different forms of neurofibroma that it might well have been included. The wisdom of including the smear technique for rapid diagnosis of the various forms of glioma may be doubted since it is only of value to those who have already had considerable experience of the gliomas and the book seems to be written for the tyro rather than the expert.

The six plates contain beautiful illustrations of the results which may be obtained by the various staining methods and should be of great value both as a guide and as an incentive to careful technique.

The Surgery of Pain. By RENÉ LERICHE. Translated by A. Young. London: Baillière, Tindall and Cox. 1939. Pp. 512. Price 21s.

The reader of Professor Leriche's book will gladly admit the truth of its translator's prefatory remark that it betrays "freshness and originality of outlook," but as he studies its pages he may also feel that these qualities are most fruitful when applied to the logical interpretation of a carefully ascertained body of fact

In other circumstances freshness and originality are too apt to lead their possessor into the wilderness of arid speculation.

Professor Leriche would be the last to deprecate criticism since he is himself a bold challenger of accepted views and their presentation, saying that modern surgical literature is often mortally dull and sometimes unreadable because of its reiterations and contradictions. No one could say that his own book is dull, though it is not free from the last-named defects.

Words are apt to have a magic quality and in these pages the word "sympathetic," both as adjective and as substantive is magical indeed in its power to provide—often with little further amplification—explanations of the causation of pain, and reasons for the failure of this and that surgical method of pain relief.

A characteristic example of the way in which the sympathetic is incriminated as a cause of pain is seen in the chapter dealing with the extremely rare condition that he calls "post-traumatic spreading neuralgia." The syndome so named has hitherto found description in French neurological literature under the title of "ascending neuritis" or "reflex paralysis" (Babinski), and an account of it may be found in this Journal (1919, 42, 349). It appears typically to result from a very minor injury to an extremity, in particular to a digit, such as a prick, a cut or even an injury not involving a breach of the skin. The clinical picture, which is painted in stronger colours by Leriche than by previous observers, includes pain of growing intensity and extent, spreading from the site of the injury proximally up the limb. The affected hand becomes moist, red and cold, the skin and nails atrophy and finally the entire limb may be severely wasted. Even more serious are the associated mental changes, for "in a very few days the patient's mental balance becomes changed" and even if we succeed in curing the pain "the brain never again becomes normal."

Leriche suggests that such a peripheral injury to a region rich in nerve endings is followed by an immediate vasomotor disorder which passing through a phase of vaso-constriction ends in passive vasodilatation. Although it is the nerve endings of the spinal nerve that are damaged, the reaction is of the sympathetic, nor is this reaction purely local for he adds that "a disordered condition of the mind materialises under our eyes, and the mechanism of its production appears to be vascular." Of the steps by which this exceedingly complex and remote reaction is brought about no very clear statement is given, nor is the explanation for the excessive rarity of this disastrous result of peripheral trauma entirely convincing. This rarity, Leriche maintains, is all a matter of individual temperament. Each person reacts in his own fashion and "we don't know why it develops in some people and not in others." It must indeed be an odd physiological mechanism that reacts in this wholly capricious and unpredictable manner.

It is perhaps in connection with the so-called spreading post-traumatic neuralgia that Leriche is least convincing, yet the order of pathological theory displayed in this chapter sets the standard obtaining elsewhere in the book. In the matter of the treatment of this syndrome he is scarcely more enlightening, for to a list of useless surgical procedures on the nervous system succeeds a list of procedures to be undertaken, and to this the general statement that none even of these is successful. "because we don't know enough."

It may well be that current physiological doctrines need constant and critical examination, but surely they cannot usefully be replaced by the invoking of "temperament" or by the easy doctrine that "each person reacts in his own fashion." This is the negation of knowledge and no advance can be looked for along this primrose path of facile speculation.

Anatomie Chirurgicale du Crâne et de L'Encéphale. Par Ch. Clavel et M. Latarjet. Paris: G. Doin. 1938. Pp. 258; figs. 151. Price 200 Fr.

This admirably written and illustrated work has been designed primarily for the neuro-surgeon, and is the fruit of a collaboration between anatomists and surgeons.

The illustrations have been drawn from anatomical specimens specially prepared for their purpose: namely, to display the topographical relationships between the skull and its contents, and between the various structures, nervous and vascular within the skull. There are also many clear radiograms in some of which post mortem lipiodol injections reveal the ventricular system and the arterial supply of the brain.

The text is clear, methodically arranged and exhaustive, and is excellently supported by the illustrations.

The authors are to be congratulated upon a fine piece of work, well planned and well executed, and one that will be as useful to the neurologist as to the neurosurgeon.

La Syphilis du Système Nerveux. By A. Sezary. Paris: Masson et Cie. 1938. Pp. 287. Price 48 Fr.

This book deals with only certain aspects of the subject from which it takes its title, and is not concerned with the clinical description of the various manifestations of nervous syphilis.

It discusses a number of the problems of neuro-syphilis, which, so far as they have any unity, have to do with the general reaction of the nervous system to the syphilitic infection.

The opening chapter deals with the state of the cerebrospinal fluid from the time of infection onward, and the course of latent syphilitic meningitis. The author then goes on to consider the etiology of nervous syphilis, and he expresses the belief (based on statistics) that adequate treatment of syphilis in its early stages renders the subject more liable to subsequent nervous involvement than no treatment at all. Dealing in the next part of the book with the pathogenesis of nervous syphilis he suggests that the central nervous system does not share in the antibody reaction which takes place in the rest of the body after infection, but that spirochætes which have lodged in it find themselves in an unfavourable medium, and take years to adapt themselves to it sufficiently to enable them to multiply freely.

He admits however that this theory, like all the other theories of the pathogenesis of G.P.I. has its weaknesses.

He is an advocate of the treatment of G.P.I. with pentavalent arsenic and considers that cases which do not respond satisfactorily to such treatment do not respond well to malaria either.

The book has many points of interest and is obviously written by one with wide experience.

Personality Structure in Schizophrenia. A Rorschach Study. By Samuel J. Beck. New York: Nervous and Mental Disease Monographs. 1938. Pp. 88. Price 2 dollars.

The writer of this monograph is prominent among those who have furthered the use of the Rorschach ink-blot method as a diagnostic aid in psychiatry. He is now concerned also to interpret what is characteristic of the schizophrenic response to the test, and thereby to gain more insight into the psychological structure of the personality of schizophrenics. His interpretations, however, depend on inferences, which may or may not be valid, as to the significance

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of particular aspects of the response, e.g. a low percentage of "good forms" in a patient's answers is taken to indicate a feeble prehension of reality. As if from falling hands, the world slips, towards which he grasps." *Ex pede Herculem* can surely be a deceptive mode of thought in these large matters of personality. Although Dr. Beck lays chief stress on this interpretative aspect of the study, more valuable are the actual findings, in a group of 81 paranoid or indeterminate schizophrenics, which he has evaluated statistically, comparing them with a group of 33 normals of about the same age and sex distribution. These useful results are presented more clearly and readably than is usual in Rorschach reports, and are well illustrated by data from individual records.

Uber Gewalttätigkeitsverbrecher und ihre Nachkommen. By KONRAD ERNST. Berlin: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie. 1938. Pp. 142. Price RM. 19·70.

This study was undertaken to throw light on the hereditary aspects of criminal behaviour in Germany, so that the question might presently by considered of whether such measures as compulsory sterilization or prohibition of marriage should be applied to criminals, as they have already been in that country to certain supposedly transmissible physical and mental disorders. The investigation cannot be said, however, to disclose anything definite: it supplies interesting social data about men who committed crimes of violence, and their children, but it does not permit any conclusion as to whether the social deficiencies of these children are mainly attributable to their environment or to hereditary factors. Ninety-three criminals, selected from a register, were the starting point of the inquiry; fourteen of them were found to have died. Their 684 wives, children, and stepchildren were investigated, nearly half of them being seen personally. The main outcome of the investigation was to confirm the general belief that the worse the parents, the worse the children, as a rule. Such factors as living in slums, having a delinquent mother, being of poor intelligence and abnormal personality, were also found to have been adverse, as would be expected.

The Postnatal Development of the Human Cerebral Cortex. Volume I. The Cortex of the Newborn. By J. L. CONEL. Cambridge, Mass.: Harvard University Press. 1939. Pp. 106, with 98 plates. Price 35s.

The present is the first volume of a work intended to trace the postnatal development of the cerebral cortex in the human subject, and deals with the cortex of the newly-born infant.

A series of clear and beautifully produced plates show the cortical appearances as seen by the cresyl violet, Cajal and Golgi-Cox methods. The text describes in detail the cell and fibre architectonics of the various cortical regions.

This work will take its place beside the familiar works of Campbell, Brodmann and Economo, and it is no unworthy member of a masterly series.

Conel finds that the definitive cytoarchitectonic pattern of the cerebral cortex, as revealed by cresyl violet staining, is already established in the normal full-term infant at birth.

The Morphology of the Brachial Plexus, with a note on the pectoral muscle and its tendon twist. By Wilfred Harris. Oxford University Press. 1939. Pp. 110. Figs. 87. Price 25s.

This book embodies the results of an extensive study of the brachial plexus throughout a wide range of the animal kingdom from Amphibia and Reptiles to Primates. In all the plexus was dissected in 158 animals and human subjects. In addition the structure of pectoralis major is studied It is found in man and some of the apes to consist of three portions, clavicular, manubrial and sterno-costal, the first-named being peculiar to man and three of the anthropoids. The twist in the tendinous insertion of the lowest portion is related to the activity of climbing and is distributed accordingly in the animal kingdom.

The supply of the dorsal aspect of the hand by the median and ulnar nerves also comes under consideration, and the author, as a result of his comparative studies, suggests that the dorsal cutaneous supply on the hand and fingers and of the dorsal interosseous muscles in man is due to latent, essentially dorsal fibres which, instead of passing into the posterior cord, are carried in the ventral cord and given off terminally in the median and ulnar nerves as in certain reptilian plexuses.

The book is illustrated by a large series of diagrams of the brachial plexus. This study, which has been carried out over a number of years, has clearly been a labour of love with Dr. Harris, who is to be congratulated upon bringing it to so fruitful a conclusion.

Hérédité et Epilepsies. Par L. Marchand. Paris: Editions de la Nouvelle Revue Critique. 1938. Pp. 123. Price 36 Fr.

In his introduction, the author points out that since in certain States measures spoken of as "eugenic" are taken in respect of "hereditary epilepsy," it becomes of increasing importance to ascertain whether, and to what extent, a heritable form of epilepsy occurs. Reviewing previous statistics, and conclusions drawn therefrom, he points out that vague and conflicting definitions of the term epilepsy vitiate most of the earlier views on this subject. The conception of an idiopathic epilepsy is becoming progressively narrowed with the advance of knowledge in pathology, physiology and biology, and it is now widely realized that epilepsy is often but one of many possible expressions of a variety of pathological changes in the brain The substitution of the term "the epilepsies" for the old term "epilepsy" expresses this changed point of view.

In the general population the proportion of so-called epileptic subjects is approximately 2 per thousand. From an analysis of all the available information, and after the exclusion of those cases due to external and adventitious factors, he concludes that there is nothing that can be called a familial epilepsy capable of direct transmission without the intervention of external factors. In congenital affections resulting from developmental defects of the ectodermal layer, epilepsy, when it is seen, is no more than a symptom of a cerebral lesion; it is symptomatic and not simply inherited.

Factors that may play a part in a familial epilepsy are syphilis, alcoholism, intoxications and other factors adverse to health, but true heredity is not in question.

SEPTEMBER, 1939

BRAIN.

PART 3, VOL. 62.

ACUTE AND SUBACUTE NECROTIC MYELITIS.

BY J. G. GREENFIELD and J. W. ALDREN TURNER

(From the National Hospital, Queen Square.)

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I.—INTRODUCTION.

IN 1926 Foix and Alajouanine published under the designation of "Subacute Necrotic Myelitis" the report of two cases characterized clinically by (1) amyotrophic paraplegia which ran a progressive course and passed from an early spastic condition to flaccidity with loss of tendon reflexes; (2) sensory loss coming on later than the paresis, at first dissociated but eventually becoming complete; (3) great excess of protein with no corresponding increase in the cell count in the cerebrospinal fluid; and (4) a subacute course leading to death in one or two years from the onset. Pathologically the lower segments of the spinal cord had undergone necrotic degeneration which affected the grey matter more than the white columns. The lumbo-sacral segments were most affected, and the degeneration became progressively less on passing upwards through the thoracic segments. This degeneration was accompanied by extreme "mesoendovascularitis" which did not, however, lead to obliteration of the lumen of the vessels. The hypertrophy of the vessels, which affected both those inside and outside the cord, did not resemble that of syphilis. They considered that the vascular disease, although more extensive than the myelitis was not primary but rather was part of a toxi-infective disease of the spinal cord.

Since this report a case of very similar type has been published by Minea (1932). This was complicated by the sudden onset of blindness five years before the paraplegia set in.

Lhermitte, Fribourg-Blanc and Kyriaco (1931) recorded under the title " La gliose angeiohypertrophique de la moelle épinière " a case of gradually progressive paraplegia which remained spastic till death and at no time showed localized muscular wasting. Van Bogaert, Ley and Brandes (1930) recorded under the original title a case of paraplegia which cleared up after an acute onset, and in which death some months later was due to cerebral complications. This case has so few points of resemblance to the original description either on the clinical or the pathological side that no useful purpose is attained by discussing it.

More acute cases, which otherwise bear some resemblance to those of Foix and Alajouanine have been published under the titles of " acute " or " subacute necrotic myelitis " by Marinesco and Draganesco (1932), van Gehuchten (1937) and Juba (1938). In none of these cases were the vascular changes so striking as in those of Foix and Alajouanine and the authors for the most part consider them as either secondary to, or as an accompaniment of, the disease of the parenchyma. Nor is it clear that these acute cases fall into a single group either from a clinical or a pathological point of view.

It seems worth while therefore to record three cases, two of which correspond very closely to those of Foix and Alajouanine both in their clinical and pathological characters, while the third, though much more acute, had sufficient clinical and pathological similarity to justify its inclusion in the same group of diseases. A survey of these cases may throw some light on the pathogenesis of the condition which appears to us to be a special and very uncommon form of disease of the spinal cord.

II.—ILLUSTRATIVE CASES.

Acute Necrotic Myelitis.

Case 1.—E. F., female, aged 37, was admitted under the care of Dr. Gordon Holmes on November 8, 1938.

Previous history: Five years before admission she had had pain in the right buttock which radiated down the back of the leg to the ankle ; this occurred in attacks lasting two weeks at a time. The pain ceased after tonsillectomy.

For some years she had had intermittent painless swelling of the knuckles.

Family history: One sister had died of malignant endocarditis and one of pulmonary tuberculosis.

Present illness: Four weeks before admission she noticed that her right leg felt dead up to the knee. There was also considerable weakness of this leg, so that when she went upstairs she had to lift it with her hands. There was no pain at first, but in the course of a few days she began to have a burning pain in the right shin, heel and toes: this came and went suddenly without obvious cause. The weakness and numbness of the right leg rapidly became worse so as to confine her to bed.

Two weeks before admission dribbling incontinence of urine began, progressing to complete retention within a week. There was also complete lack of sensation of the passage of a catheter and of fæces.

Four days before admission she first noticed that the left leg was weak, and this weakness rapidly became worse so that in the course of three days the leg became powerless. She also had girdle sensations round the upper abdomen in the four days before admission.

On examination she was flushed and looked ill. The temperature was 100·5° F. The cranial nerves and arms were normal. The intercostals and upper abdominal muscles were contracting normally but there was marked weakness of the lower abdominal muscles. Both legs were completely flaccid and no voluntary power was present in them. There was no localized wasting. The arm-jerks were normal; the knee-jerks and the right ankle-jerk were absent, but the left ankle-jerk was present. The abdominal reflexes and the plantar responses were unobtainable.

There was absolute loss of cutaneous sensation below the 10th thoracic dermatome with hyperalgesia for two segments above this. Vibration and position sense was absent in the legs and there was no tenderness of the calf muscles. No deformity or tenderness of the spine could be found on examination. The urine showed an infection by *B. coli.*

Lumbar puncture showed an initial pressure of 110 mm. with a rise to 210 mm. on bilateral jugular compression. The rise was rather slow and jerky but the fall to 110 mm. on release was normal. The cerebrospinal fluid was yellow and clotted completely on standing. It contained 18 cells per c.mm., of which 80 per cent. were polymorphs and 20 per cent. lymphocytes, and 500 mgm. of protein with marked increase in globulin. The Lange curve was 0001111221, the Wassermann reaction negative in blood and cerebrospinal fluid.

X-rays of the spine showed no abnormality.

During the next four days the upper abdominal muscles and the lower five intercostals became paralysed and the left ankle-jerk disappeared.

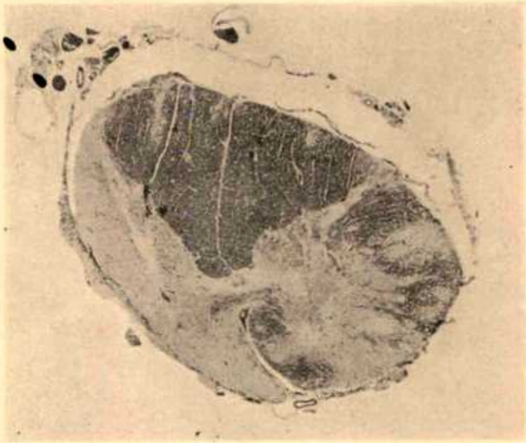
The level of cutaneous sensory loss rose so that there was marked but not complete impairment to all forms from the 8th to the 10th thoracic dermatomes with complete loss below this. There was marked hyperalgesia for about two dermatomes above the 7th thoracic.

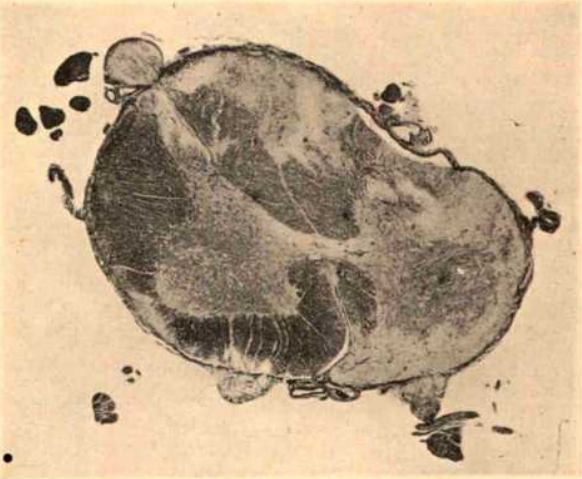
In view of the progressive nature of the disease and the possibility of an epidural abscess, a laminectomy was performed by Mr. Harvey Jackson. No abscess or tumour was found and the arachnoid and spinal cord appeared normal.

The patient died a few days after operation with a severe urinary infection and marked toxæmia.

A post-mortem examination was made within twenty-four hours of death. The organs of the body cavity appeared to be normal with the exception of the bladder and kidneys. The inner surface of the wall of the bladder was grey and gangrenous throughout and the pelves of the kidneys had a similar appearance. There was also evidence of previous nephritis in the form of adhesions and thickening of the capsule in the glomeruli.

The brain showed no macroscopical abnormality.





FIGS. 1 and 2 (*Case I*).—Sections from 11th thoracic and 3rd lumbar segments showing irregular areas of degeneration in the white columns. Loyez myelin stain.

The spinal canal was normal. In the spinal cord there was an area of greyish congestion and softening of the ventral part in the lower thoracic region, beginning in the lower part of the 8th thoracic segment and extending over about three segments. The posterior surface of the cord at this level appeared normal. The upper lumbar segments appeared relatively healthy but further softening had taken place in the 4th lumbar segment and extended from this downwards into the sacral segments.

Histological examination showed no evidence of disease in the brain, cerebellum or brain-stem except slight lymphocytic infiltration of a vein on the ventral surface of the pons. The upper cervical segments were also normal. In the 8th cervical segment a few of the small intra-medullary vessels had rather thickened walls, and one nerve cell in the anterior horns was swollen and chromatolytic with an eccentric nucleus. No abnormality was seen on descending through the thoracic segments until the 7th segment was reached. From this level downwards patches of degeneration were present in the white columns (figs. 1 and 2). These varied in appearance and could be divided fairly sharply into three types. The first, which is here called *lacunar degeneration*, consisted of the formation of fairly large lacunæ which appeared to arise from distension of the myelin sheaths. Many contained a greatly swollen axis cylinder and in a few the pyknotic nucleus and small irregular cell body of a myeloclast could be seen. Areas of this kind showed no evidence of cellular increase. They resembled the lacunar areas seen in the lateral columns of the cord in cases of extrathecal carcinoma, but were larger, tending to spread round the margin of the cord. In the second type, which was probably a later stage of the same process, the tissues were heavily infiltrated with microglial cells, most of which were swollen with lipoid in various stages of katabolism. In these areas there was always a tendency for collagen fibres to spread out from the walls of the vessels, and in some there was a considerable fibrosis of this kind. This type or stage of degeneration is here called *mesodermal reaction* to distinguish it from the third stage which is that of *frank necrosis* of all the tissues. In necrotic areas very few nuclei were visible, and these were degenerated or pyknotic. They appeared to belong chiefly to microglial cells, but a few had the multilobar appearance of polymorphonuclear leucocytes. The vessels in these areas were also degenerated with no nuclei in their walls. A few swollen axis cylinders could be seen in these areas. It was noted that an area of necrosis was always associated with a zone of less intense degeneration above, below, and round it. The three types of degeneration appeared therefore to represent different stages in the necrotic process. The lacunar type probably represented the earliest stage which might progress either to the type with mesenchymal reaction, or to frank necrosis according to the intensity of the process. It was difficult to be certain whether the mesenchymal type of degeneration could progress to the necrotic type, owing to the difficulty of distinguishing the different kinds of tissue in a necrotic area. There seemed, however, no doubt that lacunar degeneration might pass directly into necrosis without going through the stage of mesenchymal reaction.

In the 7th thoracic segment, areas of lacunar degeneration with early mesodermal reaction were present in both lateral columns and were continuous with fairly large areas of necrosis in these columns in the 8th and 9th segments.

In the 10th thoracic segment the degeneration was less intense being chiefly of lacunar type with a narrow zone of mesenchymal reaction on the surface of the ventral columns. In the 11th thoracic segment a patch of necrosis appeared in the region of the left pyramidal tract. It was surrounded by a zone of mesodermal reaction which swung round the surface of the antero-lateral columns. In this segment a small area of vacuolar degeneration appeared in the left dorsal column, which above this level had only shown the early stages of Wallerian degeneration in the column of Goll. In the 12th thoracic segment and in the upper three lumbar segments the degeneration was chiefly of lacunar type with early mesodermal reaction. On passing downwards through these segments the patches of degeneration tended to leave the antero-lateral columns and to appear more in the dorsal columns. In the 4th lumbar segment the dorsal columns were the seat of frankly necrotic degeneration which in the 5th lumbar segment spread round the dorsal horns to the margins of the antero-lateral columns. The sacral segments were very slightly affected.

The grey horns showed some degeneration chiefly of lacunar type and in the lower lumbar segments were invaded by areas of mesodermal reaction with complete disappearance of myelinated fibres. Only in a few places did this lesion pass deeply into the grey matter, for example the ventral horn on one side in the 5th lumbar segment was almost entirely involved in degeneration of this type. More often the margins of the horns were degenerated, so that the grey matter was separated by a zone of mesodermal reaction from the necrotic white columns.

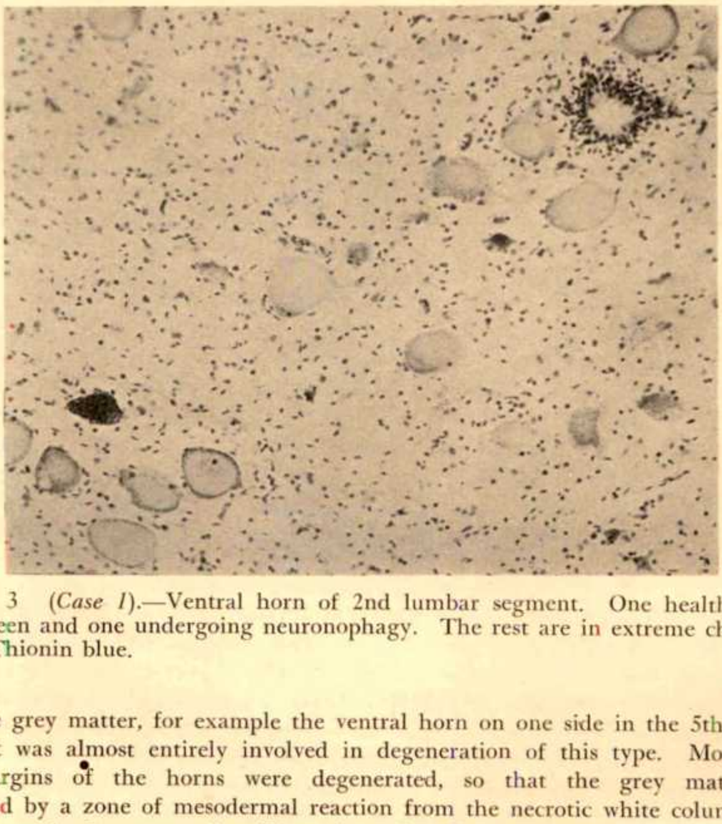


FIG. 3 (*Case I*).—Ventral horn of 2nd lumbar segment. One healthy nerve cell is seen and one undergoing neuronophagy. The rest are in extreme chromatolysis. Thionin blue.

Changes in the nerve cells.—Throughout the affected segments the nerve cells of the ventral and dorsal horns, including those of Clarke's column, were greatly swollen and devoid of Nissl granules. Their appearance was that of a very severe axonal reaction and could be largely accounted for by degeneration of the white matter through which their axones passed. In the third lumbar segment the ventral columns on one side were normal while the majority of the neurones of the corresponding ventral horn were chromatolytic, but this could be accounted for by severe degeneration, due to vascular occlusion, in the ventral root. In the 4th and 5th lumbar segments the nerve cells were less universally affected and in the sacral segments almost all were normal. In the most affected segments a few of the nerve cells had undergone neuronophagy and were replaced by a ring of microglial nuclei (fig. 3). This fact, and the extreme swelling of all the neurones in these segments suggested that ischæmia of the tissues played some part in this process.

Vascular changes.—Associated with these degenerative changes in the parenchyma of the cord there were very definite alterations in the pial vessels. These began to be evident in the lower half of the thoracic level and here were confined to the small dorsolateral vessels, many of which were obliterated or had their lumen greatly reduced by hyaline thickening of their walls (fig. 4). Weigert's stain showed a fine layer of elastin usually internal to the zone of hyaline thickening but in a few cases external to it. These vessels therefore appeared to be fine arteries. Most of the larger arteries appeared normal, except for reduplication of their elastic lamina. The large radicular veins were healthy except for varying degrees of lymphocytic infiltration in and around their walls. The vessels inside the cord were less affected, but many, especially in the lumbar segments, were thickened or almost obliterated with connective tissue and their number appeared to be increased. In the lumbar segments also the small vessels in the ventral roots were similarly or more severely affected, many being completely obliterated. Here both arteries and veins appeared to be involved. The myelinated fibres of these roots were severely degenerated. A large anterior spinal vein at the level of the third lumbar segment showed considerable hyaline thickening of its intima, but its lumen was not noticeably reduced. Apart from this the larger vessels appeared intact.

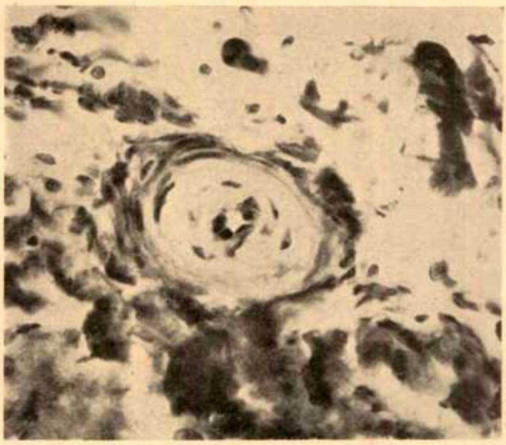


FIG. 4 (*Case I*).—11th thoracic segment. Small meningeal vessel almost obliterated by hyaline thickening. Iron hæmatoxylin, van Gieson.

SUMMARY OF PATHOLOGICAL FINDINGS IN CASE 1.

Degeneration of the white columns of the spinal cord of a patchy character was found from the 7th thoracic segment downwards to the lower segments of the lumbar cord. It varied in degree from lacunar degeneration to frank necrosis. In the lower thoracic segments it tended to affect the anterolateral columns more than the dorsal columns whereas in the lumbar segments this order was reversed. This degeneration was associated with hyaline thickening of the small arteries and veins on the surface of the cord and as they entered it. The relationship between necrosis and sclerosis of the small vessels appeared very intimate since the meninges overlying areas of necrosis usually contained one or more small vessels with their lumen obliterated or greatly reduced. Degeneration of the roots also was associated with similar sclerosis of their small vessels. This sclerosis, which might involve the intima but more often the media, appeared to affect small arteries more than veins, though in some no elastic lamina could be made out. The larger parent vessels appeared normal except for occasional reduplication of the elastic lamina in the arteries and for perivascular infiltration of the veins, both outside and inside the cord. An occasional medium or larger sized vessel showed early hyaline thickening of its inner coat. The infiltration varied in intensity from one segment to another, and may have been due, in part at least, to the laminectomy. Throughout the affected segments the nerve cells showed intense chromatolytic swelling with occasional neuronophagy.

Subacute Necrotic Myelitis.

Case 2.—G. C., male, aged 55, a bailiff, was admitted under the care of Dr. Kinnier Wilson on February 11, 1937.

Previous history: At the age of 21 he had gonorrhœa, and when 43 he suddenly developed auricular fibrillation after running in a race ; this persisted but had been controlled with digitalis. Since the age of 43 he had had several attacks of acute gout, and there was a strong history of gout in his family.

Present illness: Seven months before admission, he had felt numbness on the front of the left thigh, which in the course of two to three weeks spread to the calf, the outer side of the leg and the sole of the foot. At first the numbness was intermittent but soon it became continuous. A month late numbness appeared in the right leg in the same distribution and at the same time he began to have difficulty in walking, having to force his legs along the ground, and he also had some involuntary jumping of his legs at night.

Four and a half months before admission he was confined to bed with an attack of acute gout, and when he was able to get up he found that his legs were much weaker than before and that he could not walk more than 200 yards at a stretch. Within the next week he developed difficulty in starting micturition, and the stream became less forcible ; also he had trouble with defæcation, having to strain to pass a motion. This was followed by numbness of the tip of the penis and within the next few weeks by numbness of the back of the thighs and of the buttocks. There was no pain at any time.

On examination he was a healthy-looking, rather obese man. There was a gouty tophus in the left ear and thickening of the left olecranon bursa, also swelling of the tarso- metatarsal joints of both great toes. The heart was not enlarged clinically. The pulse was 80 per minute with auricular fibrillation, blood-pressure 150/100. The peripheral arteries were not abnormally thickened. There was slight œdema of the ankles.

Neurological examination.—No abnormality was found in the cranial nerves or arms.

Motor system: There was slight wasting of the quadriceps groups on both sides relatively to the rest of the legs. No fibrillation was observed. Tone was increased in the legs. Power was moderately diminished in both legs, the right being rather weaker than the left. Flexion of the right hip was relatively the weakest movement.

Reflexes: The arm-jerks were normal. The upper abdominal reflexes were weak, the lower absent. The knee and ankle-jerks were much increased and the plantars extensor.

Sensation: There was hypalgesia up to the 9th thoracic dermatome on both sides, the impairment being most marked from the 4th lumbar to the 1st sacral. There was slight impairment to light touch in both legs below the knees. Vibration was not felt on the knees or ankles, and was just felt on the iliac crests. Position sense was much impaired in the feet.

The gait was moderately spastic with some ataxia but walking without support was possible.

Investigations.—Lumbar puncture: The initial pressure was 210 mm. with a normal rise on jugular compression.

The cerebrospinal fluid was clear and colourless. It contained 1 cell per c.mm. and 100 mgm. per cent. of protein. It gave a very weakly positive Pandy reaction, and a negative Lange reaction.

The Wassermann reaction was negative in blood and cerebrospinal fluid.

The test meal showed normal free acid. The blood count was normal. The blood uric acid was 4·7 mgm. per cent.

X-ray examination of the spine showed moderate osteo-arthritis, but no other abnormality.

Cisternal puncture was done and the cerebrospinal fluid contained 45 mgm. per cent. of protein. Lipiodol was injected and descended without any evidence of block.

During the next six weeks his legs became weaker so that he was unable to walk, and on examination it was found that the sensory level had risen to the 7th thoracic level and that light touches with cotton-wool were not felt below this level; there was also impairment to pin-prick.

A laminectomy was decided on and on April 13, 1937, Mr. Julian Taylor operated. The laminæ from D.4 to 7 were removed, there was no sign of extra- or intramedullary tumour, but an unusually tortuous vessel was seen on the dorsal surface of the cord. There was a free flow of cerebrospinal fluid on jugular compression.

The patient died five days after operation.

A post-mortem examination was made twenty-four hours after death. The brain was macroscopically normal. The arteries at the base were healthy with the exception of slight atheroma of the internal carotid arteries at their passage through the dura matter. There was no evidence of narrowing of the spinal canal. The spinal cord as a whole looked small considering the patient's build and was of rather varying consistency in the lower thoracic and upper lumbar segments.

Examination of the chest showed no abnormality in the lungs except slight superficial collapse. The pericardium contained an ounce of yellow serous fluid. The epicardial surface of the heart was covered by a greyish irregular membrane which suggested a non-adhesive pericarditis of old standing. The heart was large and fatty with dilated chambers and valvular orifices, but with no valvular disease. Irregular patches of atheroma with one or two small areas of calcification were present on the coronary arteries, the aorta was dotted with yellowish plaques from the aortic valves upwards and there was severe atheromatous ulceration in its lower abdominal portion. The liver was large and appeared normal ; the gall-bladder contained several small pigmented calculi and pale bile. The kidneys were large with fœtal lobulation and arteries which gaped more than normal. Their capsule was adherent to the surrounding tissues but stripped easily from the kidneys. The other organs of the body appeared healthy.

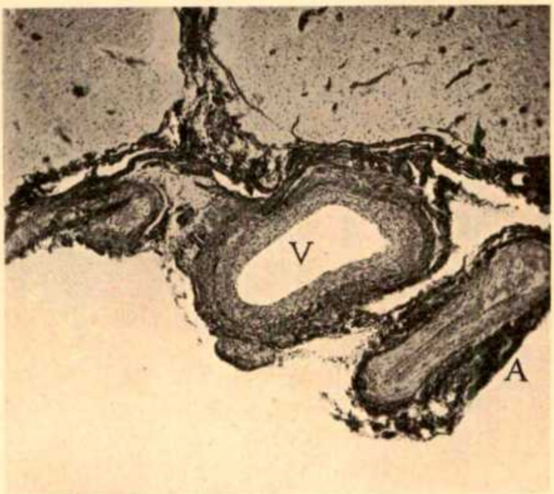


FIG. 5 (*Case* 2).—Anterior spinal artery and vein from the 3rd lumbar segment. The vein is much thicker than the artery which, except for some adventitial thickening, is normal. Iron hæmatoxylin, van Gieson.

Histologically, some patchy epicardial lymphocytic infiltration was found in the heart, and an occasional small vessel showed some evidence of endothelial proliferation. Slight lymphocytic infiltration was also seen in the portal spaces of the liver and there was a slight degree of fatty infiltration. The kidneys showed no degenerative changes beyond those common at this age, viz. sclerosis of a few glomeruli and slight interstitial sclerosis. In the *brain* the only noteworthy changes were calcification of some of the small vessels in the cornu Ammonis between the fascia dentata and Sommer's sector. The only other abnormality was a slight variation in the thickness of the adventitial coat of the superficial veins which was no greater than is commonly seen. The brain-stem and cerebellum showed no other abnormality.

Spinal Cord.—In the cervical and first three thoracic segments the only abnormality seen was degeneration of the column of Goll, associated with some fibrous thickening of the veins in the postero-median septum. In the 4th thoracic segment the small vessels in the ventrolateral column appeared more prominent than normal owing to slight thickening of their walls. In the 5th, 6th and 7th thoracic segments the veins on the dorsal surface began to show irregular or eccentric thickening of their walls, and from the 8th thoracic segment downwards the large anterior spinal veins were greatly thickened in a concentric manner so that at first sight they appeared to be arteries ; they were indeed considerably thicker than the accompanying arteries which retained their normal appearance (fig. 5). Along with this thickening of the superficial veins there was also a fibrous thickening of the walls of the small intramedullary vessels which became progressively greater on passing downwards through the last five thoracic segments, and remained of the same intensity through the upper lumbar segments, especially in the ventral horns. It diminished in the lowest lumbar and disappeared in the sacral segments. In the lower lumbar segments small perivascular hæmorrhages were seen here and there in the ventral horns. In and beside them were a few lymphocytes and mononuclear cells containing blood pigment.

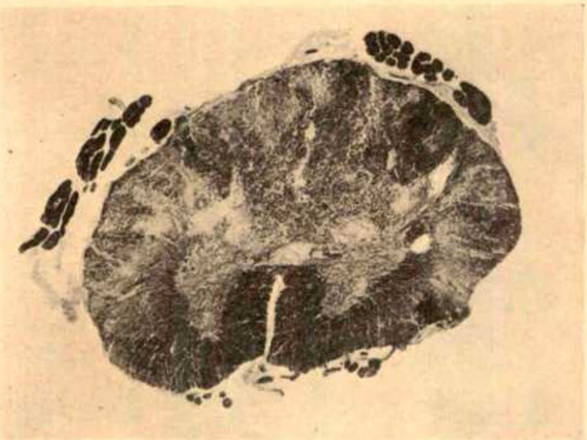


FIG. 6 (*Case* 2).—Section of 11th thoracic segment showing irregular and incomplete degeneration of the grey and white matter. Weigert-Pal method.

No definite primary focus of degeneration of the parenchyma of the cord could be made out in the upper ten thoracic segments. Lacunar degeneration was first seen in the 11th thoracic segment on the right margin of the dorsomedian septum near the surface of the cord and on the surface of the left lateral column (fig. 6). In the latter situation it had progressed to central necrosis and was associated with great thickening of the small vessels in the white matter, some of which formed small glomerular masses. In the 12th thoracic segment small isolated areas of necrosis surrounded by a narrow zone of fenestration were present in both lateral columns. In the 1st lumbar segment several areas of lacunar degeneration, some of which had progressed to central necrosis were present in the dorsal columns. In the 2nd to 5th lumbar segments very little primary degeneration was seen in the white columns, but scattered small areas of myelin destruction without any fenestration of the tissues were seen in the ventral horns and the bases of the dorsal horns. There was, however, little evidence of degeneration of the nerve cells except for chromatolysis in isolated cells in the ventral horns. Most of the cells of Clarke's column in the last two thoracic and first lumbar segments also showed chromatolytic changes which could be accounted for by the degeneration of the lateral columns at these levels.

Case 3.—J. G., male, aged 61, a shopkeeper, was admitted under the care of Dr. C. P. Symonds on January 24, 1938. His past history was uneventful.

The present illness began nine months before admission with pain in the right calf and the back of the right knee and thigh. This pain was a continuous dull ache, worse when walking and relieved to some extent by resting. It gradually became worse and was severe enough to make him limp at times; during a three weeks' holiday it became less severe, only to increase on returning to work. Three months later pain appeared in the left leg behind the knee and in the calf but not in the thigh; the character of the pain was the same as in the right leg.

Six months later he noticed that the legs, especially the right, were becoming weaker, and because of the increasing pain and weakness he had to give up work.

Two and a half months before admission difficulty in passing water developed and on one occasion there was retention which was overcome by local heat. The weakness of his legs rapidly became worse; they began to feel stiff and he had frequent painful flexor spasms. He was confined to bed for a fortnight before he was admitted and had developed complete retention of urine, needing catheterization for a week.

He admitted to some numbness of both feet during the preceding three months and to occasional numbness of the finger-tips during the previous fortnight.

On examination he was in considerable pain and was having frequent painful flexor spasms.

The heart was normal. Blood-pressure 190/100. The peripheral arteries were not abnormally thickened.

Neurological examination.—The cranial nerves and arms were normal.

Motor system: He had to be supported when sitting up. The legs were generally rather thin but there was no localized wasting and no fibrillation. Tone was slightly increased in both legs. Power was greatly reduced in all movements of both legs, the left leg being the weaker of the two. Peripheral movements were relatively more affected than proximal ones.

Reflexes.—The arm-jerks were normal, the upper abdominals weak; the lower absent; the knee and ankle jerks were absent; the right plantar was extensor and the left was a doubtful extensor.

Sensory system: No cutaneous sensory loss was found. Position sense was completely absent in the feet. Vibration was much diminished on the iliac crests and patellæ, and was more severely impaired though just present on the malleoli. The calf muscles were very tender.

Investigations.—*Lumbar puncture*: The initial pressure was 130 mm. with a free rise on jugular compression. The cerebrospinal fluid contained 3 cells per c.mm. and 70 mg. per cent. of protein. There was no excess of globulin and no change in the Lange reaction. The Wassermann reaction was negative in blood and cerebrospinal fluid.

Urine: *B. coli* infection.

Blood count: Red blood cells, 4,580,000; hæmoglobin, 82 per cent.; white blood cells, 10,800.

Test meal: Normal free acid.

In the course of the next two or three weeks the weakness of the legs increased, they became flaccid and the plantar responses were unobtainable. Pain and tenderness of the legs remained a prominent symptom.

A fortnight after admission he vomited half a pint of blood and his hæmoglobin was reduced to 42 per cent.

Later he developed a severe urinary infection and became uræmic. His confused mental condition (apparently due to uræmia) made sensory testing difficult, but no definite sensory loss was found till about two months after admission, when he had complete analgesia and anæsthesia below the middle of both thighs with some impairment to pin-prick above this up to the 10th thoracic level.

Sense of position and of vibration were completely absent in the legs. There was progressive generalized wasting of the legs but no localized wasting ; the knee and ankle jerks remained absent and the plantars unobtainable.

Electrical reactions showed partial R.D. in all muscles of both legs, more marked below the knees.

A lumbar puncture on April 12, 1938, gave an initial pressure of 30 mm. with free rise on jugular compression.

The cerebrospinal fluid was very faintly straw-coloured. It contained no cells and 100 mgm. per cent. of protein.

He died on April 12, twelve months after the onset of symptoms.

A post-mortem examination was made one hour after death. The body was that of a wasted elderly man with necrotic sacral decubitus. The legs were especially wasted.

The brain showed no external abnormality except dilatation of the basilar artery and patches of atheroma on the branches of the middle cerebral arteries.

In the *spinal cord* the dorsal roots of the lumbo-sacral enlargement looked rather grey ; the ventral roots appeared to be normal. Apart from this the cord looked normal macroscopically.

In *the heart* a mass of tough clot was found in the right auricle and ventricle and was found to be continuous with clot in the inferior vena cava and the left renal vein in which it was very adherent, brown and friable. Apart from this the heart was normal. The aorta showed slight atheroma in its thoracic part which became progressively greater on passing down the abdominal portion. The pelves of the kidneys were distended with purulent urine, but only one or two small early abscesses could be seen in the substance of the kidneys. The bladder wall was inflamed. In the first part of the duodenum just beyond the pylorus there was a small peptic ulcer. The other organs were healthy.

Histologically, the base of the duodenal ulcer contained several vessels with greatly thickened walls. These appeared to be both arteries and veins, and as the inflammation at the base of the ulcer reached almost down to them it may well have been the cause of the thickening of their walls.

In the *heart* wall several small arteries showed irregular thickening of their walls. The anterior coronary artery was grossly thickened by atheroma with calcification and deposition of cholesterin crystals in the plaques. In the *spleen* there was also some thickening of the small Malpighian arteries. The *kidneys* showed considerable thickening of the capsule, sclerosis of glomeruli and cellular fibrosis of a patchy character.

There was little abnormality in the *brain* except slight thickening of the walls

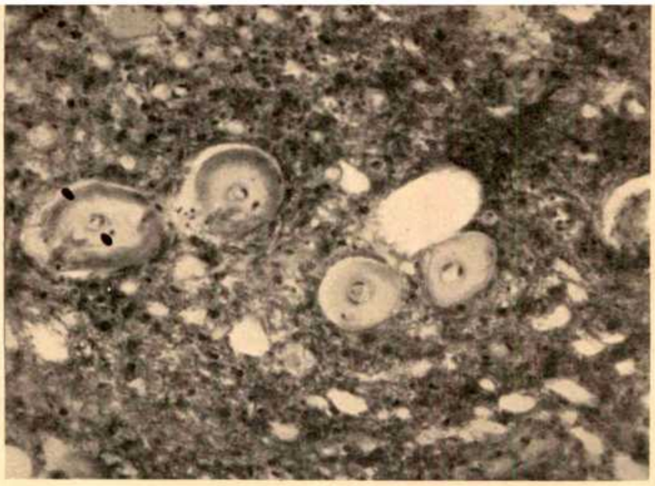


FIG. 7 (*Case 3*).—Small vessels in the base of the dorsal horn of the 12th thoracic segment showing great hyaline thickening of their walls. They are surrounded by dense neuroglial overgrowth. Phosphotungstic acid hæmatoxylin.

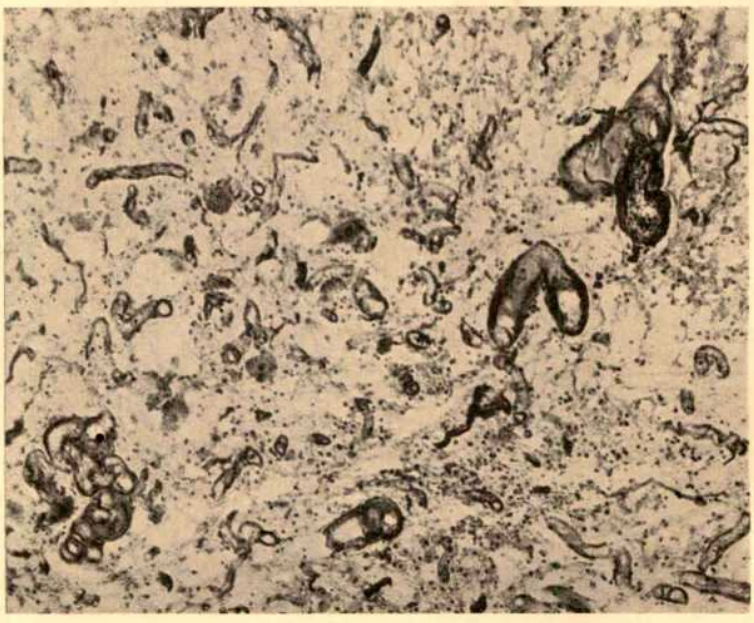


FIG. 8 (*Case 3*).—Part of ventral horn of the 4th lumbar segment showing thickening and tortuosity of the small vessels and lacunar degeneration of the tissues. A few normal nerve cells are seen. Iron hæmatoxylin, van Gieson.

of some of the small cortical vessels. This had not, however, caused any "areas of paling." The basal ganglia and brain-stem were normal. A small vein running round the surface of the cerebellum had its wall irregularly thickened by hyaline fibrous tissue.

Spinal cord.—*Vascular changes*: Throughout the cervical segments considerable connective tissue overgrowth was present in the veins of the posteromedian septum. In the first thoracic segment several dilated vessels were present within and just anterior to the tip of the dorsal horn on one side. In the 3rd to the 5th thoracic segments the small veins both on the ventral and dorsal surface were greatly thickened in a concentric manner with connective tissue. In some the lumen was only just patent. At the 6th thoracic level the vein in the posteromedian septum and a vein in one lateral column were almost occluded by thickening. At the 8th and 9th thoracic levels a tangle of thick-walled veins was present on the dorsal surface of the cord and the vessels in the anterior horn on the same side were greatly dilated.

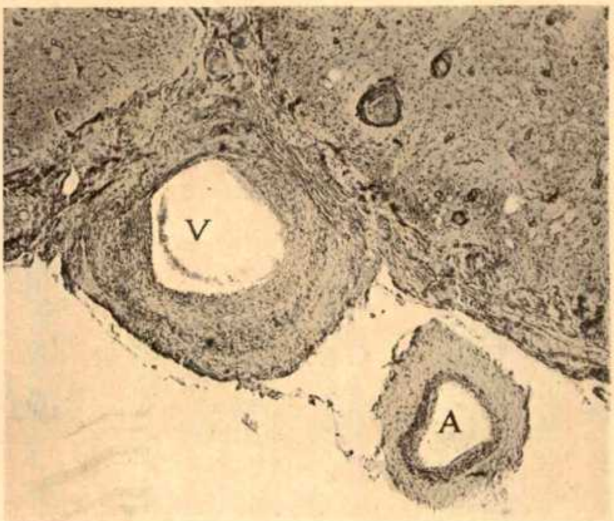
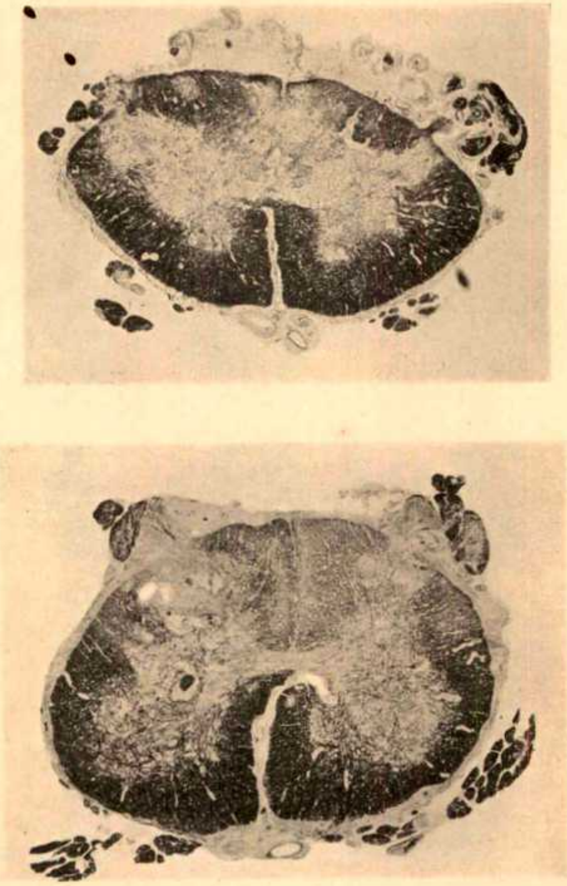


FIG. 9 (*Case 3*).—Anterior spinal artery and vein from the 4th lumbar segment. The vein has greatly thickened walls, while the artery shows only adventitial thickening. Iron hæmatoxylin, van Gieson.

Throughout the lower four thoracic and the first lumbar segments the intramedullary vessels were greatly thickened and appeared to be much more numerous than normal, especially in the grey matter of the ventral and dorsal horns. A few were completely occluded (figs. 7 and 8). There was also concentric thickening of the veins on the ventral and dorsal surfaces of the cord. Those on the dorsal surface were especially thickened, and at the 11th and 12th thoracic levels one was occluded by fibrous thickening. In the other lumbar segments the intramedullary vessels were less severely affected, although still very abnormal. The anterior spinal veins were thickened down to the conus terminalis, but their lumen was not reduced (fig. 9).

Parenchymatous degeneration.—In the cervical and upper thoracic segments the only degeneration of the white columns of the cord was Wallerian degeneration involving most of the fibres in the column of Goll. Primary degeneration of a lacunar type appeared in the dorsal columns, in the 8th and 9th thoracic segments. In the 10th and 11th thoracic segments isolated rounded areas of myelin degeneration and fenestration of the tissues appeared in the antero-lateral columns, as well as the dorsal columns. In these segments the grey matter appeared intact. In the 12th thoracic and all the lumbar and sacral segments there were patches of myelin destruction in the ventral and dorsal horns which were also surrounded by a zone of lacunar degeneration of the white matter or by small areas devoid of nuclei and suggesting early necrosis. The white matter towards the surface of the ventrolateral columns was less affected, except for small isolated foci of lacunar degeneration and for



FIGS. 10 and 11 (*Case 3*).—Section of 12th thoracic and 3rd lumbar segments showing irregular areas of degeneration in the grey and white matter. Weigert-Pal method.

Wallerian degeneration of the pyramidal tracts (figs. 10 and 11). The dorsal columns had lost a large proportion of their fibres throughout the lumbar segments. This appeared to be due partly to isolated rounded foci of primary degeneration and partly to degeneration of the dorsal roots, in some of which patches of degeneration were present. The nerve cells throughout the affected segments were remarkably healthy; a few showed a moderate degree of chromatolysis, but there was no neuronophagy or other definite evidence of disappearance of nerve cells. There was dense neuroglial sclerosis in the affected regions of the cord.

III.—CLINICAL FEATURES.

Clinically the cases of necrotic myelitis fall into two distinct groups, the *acute group,* represented by our first case and the cases of van Gehuchten and Juba; and a *subacute group,* represented by the original two cases of Foix and Alajouanine, by our second and third cases, by Minea's case, and by the case of Lhermitte, Fribourg-Blanc and Kyriaco which is a more chronic example of this group. These cases will be considered as a basis for outlining the clinical characteristics of the disease.

(*a*) *Acute Necrotic Myelitis.*

This shows itself by a rapid destruction of function of the spinal cord in the lumbar and sacral segments, with, in our case, at least, a fairly rapid ascent of the signs to the lower dorsal segments. Owing to the rapidity of disturbance of function of the cord a flaccid paraplegia develops, and in none of the recorded cases has there been any sign of recovery from this.

Detailed analysis of symptoms and signs.—Age and sex: Two patients were women, aged 37 and 34, and the other was a man aged 47.

Previous health: Four years before, during pregnancy, van Gehuchten's patient had had a sudden onset of flaccid paraplegia which ascended in the course of a few days to involve the arms; this was accompanied by sensory changes, but apparently not by sphincter disturbance. The flaccidity slowly gave way to spasticity, and in the course of a few months the patient was well again.

The other two patients had uneventful previous histories.

Disturbance of motor function.—The time taken for the development of paraplegia has varied a little in the three recorded cases. In our patient the right leg in the course of two to three days became so weak that she had to lift it with her hands when she went upstairs, and it was not till nearly three weeks later that the left leg started to become weak. During the next week while under observation there was some ascent of the paralysis, and the upper abdominal and lower intercostal muscles, which had previously been contracting normally, became paralysed.

In Juba's patient both legs became weak at about the same time, and the weakness progressed so rapidly during the next week that he was unable to stand: he was examined a few days after this and there was a complete flaccid paraplegia with absent reflexes and absence of plantar responses.

The onset of complete paralysis was more rapid still in the patient recorded by van Gehuchten, as flaccid paraplegia developed in the course of forty-eight hours. No ascent of the paralysis is mentioned by either of these authors.

Sensory changes.—Subjective sensory symptoms have not been a prominent feature of the disease; pain of a burning type in the right leg was complained of in the early part of our patient's illness, but this was not severe and passed off after a few days. Juba's patient also complained of sharp pains in both legs, which preceded the onset of weakness by about a fortnight.

Objective evidence of sensory loss has been present early in all three cases; our patient lost sensation in the right leg at about the same time as the motor symptoms started, and three weeks later when she was examined there was complete loss of all forms of sensation below the 10th thoracic segment on both sides, with a narrow band of hyperalgesia above this. During the next week, accompanying the ascent of paralysis, cutaneous sensation became impaired, though not completely lost, from the 8th to the 10th thoracic levels with hyperalgesia for two segments above this.

In van Gehuchten's case there was a band of hyperæsthesia at about the level of the umbilicus with sensory loss to all forms below the 11th thoracic dermatome. Juba's patient had sensory loss below the 12th thoracic segment, but apparently no hyperalgesia. No ascent of the sensory loss is described in these two cases.

Sphincter disturbance.—This has been present as an early symptom in all the acute cases of the disease, and incontinence has always appeared within a fortnight of the onset of weakness.

Cerebrospinal fluid.—There have been marked changes in the fluid in all three cases, consisting of considerable increase in protein and cellular content. In our case the initial pressure was normal; although, the rise on jugular compression was only to 210 mm. and was distinctly slow, the fall on jugular release was at a normal rate. The fluid was yellow and clotted spontaneously, the protein content being 500 mgm. per cent. and the cells 18 per c.mm., of which 80 per cent. were polymorphs and 20 per cent. lymphocytes.

In both the other cases the protein content was high, in Juba's the globulin reactions were strongly positive and in van Gehuchten's the protein was 1,000 mgm. per cent.; in the former there were 680 cells per c.mm. and in the latter case many lymphocytes were found.

(*b*) *Subacute Necrotic Myelitis.*

Clinical aspects.—The clinical account of the subacute type of the disease has been derived from our second and third cases, from the original two cases of Foix and Alajouanine (1926), from Minea's case and from the case of Lhermitte *et alii.*

Subacute necrotic myelitis is a disease of gradual onset and slowly progressive course, usually without any remission, though in one case there was some recovery of power in the legs for two to three months. The presenting symptom is usually weakness of the legs, though this may be preceded by severe pain in the distribution of the sacral segments or by dysæsthesiæ in the lumbar and sacral areas.

Previous history and evidence of associated disease.—In both the cases of Foix and Alajouanine there was a history of albuminuria some years before, though no details of this are given; while one of their patients who was a plumber had suffered from lead colic.

In our second case there was a family history of gout and the man himself had had several attacks of acute gout in the eight years preceding his illness. He also had cardiovascular disease, causing auricular fibrillation twelve years before, which was well controlled with digitalis. His blood-pressure was 150/100.

Our third case had a blood-pressure of 190/100 on admission, though this fell later in his illness. Death was due to pulmonary embolism, secondary to phlebitis of the left renal vein.

In Lhermitte's case the first symptoms followed an attack of phlebotomous fever.

No history or evidence of syphilis was present in any of the cases. All six have occurred in males, whose ages at the time of onset were 23, 27, 29, 50, 55 and 61 years.

Visual symptoms.—A point of special interest in Minea's case was a rapid loss of vision, chiefly in the right eye, five years before the onset of paralysis. This was proved to have the same pathological basis as the spinal symptoms and therefore must be reckoned as an integral part of the clinical picture in this case. In the second case of Foix and Alajouanine papillitis appeared late in the disease but no pathological changes were found in the optic nerves to account for this.

Disturbance of motor function.—The clinical picture will depend on the time after the onset at which the patient is first seen and on the rapidity with which the functions of the spinal cord are destroyed, this is well illustrated by the five cases under consideration. At one end of the scale is Lhermitte's case which showed a spastic paraplegia without localized wasting, while at the other end are our third case and Foix and Alajouanine's second case, in both of which there was a flaccid paraplegia with absent tendon-jerks but with frequent flexor spasms. In both these cases flexor spasms soon stopped and a complete flaccid paralysis of the legs developed. The other cases showed intermediate pictures of the disease; our second case had a spastic paraplegia with wasting of the thigh muscles, and in this case a flaccid stage never developed, but as he died after a laminectomy performed nine months after the onset of the illness, it is probable that the natural history of the disease was terminated prematurely. The French authors' first case showed a somewhat similar picture but in the course of a few months the tendon-jerks disappeared, localized wasting of the thighs and buttocks became more marked, and voluntary power in the legs was completely lost. In Minea's case at the time of examination there was complete flaccid paralysis, but the knee-jerks and the right ankle-jerk were preserved although greatly diminished. Œdema of the legs masked any wasting that might have been present.

Sensory changes.—Pain has not been a marked feature except in our third case in which it was the presenting system and was persistent practically till the death of the patient.

The type of sensory impairment found in all the cases, except that of Lhermitte, has certain characteristic features. It occurs a considerable time after weakness is complained of; in one of the original French cases there was an interval of seventeen months between the onset of weakness and the discovery of sensory impairment. When sensory changes first appear pin-prick and temperature appreciation are considerably more affected than appreciation of touch and the first places in which impairment is found are the lower lumbar and sacral segments. As the disease progresses there is a definite ascent of the sensory level on to the abdominal wall and appreciation of touch becomes more affected than it was at first; even in the later stages, however, the impairment to pain and temperature is more marked and more extensive than it is for touch. Deep sensibility is severely affected, and this may occur before there is any impairment of cutaneous sensibility. In one case, at least, there was considerable tenderness of the calf muscles accompanying the loss of position sense.

Lhermitte's case was the only one which did not show any ascent of the sensory level whilst the patient was under observation.

Sphincter disturbance.—Trouble with micturition has occurred early in the course of the disease, in no case later than six months from the first symptom, and usually consists of some difficulty in starting to pass water and, a month or so later, retention needing catheterization.

Cerebrospinal fluid.—The most constant change in the cerebrospinal fluid is increase in protein; in the original French cases a moderate lymphocytosis was found but the actual cell counts are not mentioned. In the first French case a lumbar puncture was done six months from the first symptom, and the cerebrospinal fluid was found to be quite normal: when this puncture was repeated eleven months later there was a marked increase of protein and a slight lymphocytosis, while four months later still the amount of protein was said to be massive and the lymphocytosis moderate. An interesting observation made by Foix and Alajouanine in this case is that a second puncture was done in the dorsal region apparently above the level of the lesion in the spinal cord and the cerebrospinal fluid from this site also contained a considerable amount of protein. Their second case showed changes in the cerebrospinal fluid at a considerably earlier stage as a puncture done two months from the onset gave a yellow fluid with a large amount of albumin and some increase of lymphocytes. The fluid of Lhermitte's patient contained great excess of protein and 40 lymphocytes per c.mm. In Minea's case the fluid was slightly yellow, contained 46 cells per c.mm. and gave a positive Nonne-Apelt reaction.

In our cases the excess of protein although definite was not great; in our second case a puncture was done seven months after dysæsthesiæ were complained of in the legs, and the cerebrospinal fluid protein was 100 mgm. per cent. and there was 1 cell per c.mm.; a cisternal puncture gave cerebrospinal fluid with a protein of 45 mgm. per cent. Puncture on our third case was done nine months after the pains started and three months after weakness of the legs was complained of; at that time the cerebrospinal fluid protein was 70 mgm. per cent. and there were 3 cells per c.mm. A second puncture was done three months later and then the cerebrospinal fluid was faintly straw-coloured and the protein was 1·00 mgm. per cent. In both our cases the Queckenstedt test showed no evidence of spinal block, and in the first case lipiodol injected into the cisterna magna passed freely to the lower end of the subarachnoid space.

Other Special Investigations.

Both our cases had normal percentages of acid in the gastric juice and the blood-counts were within normal limits. The white blood cells were 10,800 in the third case, but this was probably due to urinary infection.

X-rays of the spine showed no abnormality except for moderate osteo-arthritis in one of the cases.

IV.—DIFFERENTIAL DIAGNOSIS.

The differential diagnosis of acute necrotic myelitis presents considerable difficulty, and, while syphilitic transverse myelitis may be excluded by the absence of a positive Wassermann reaction, other types of acute myelitis, especially those due to the demyelinating diseases are likely to cause confusion. In neuro-myelitis optica the development of the spinal lesion may precede by a considerable period the ocular symptoms and when paraplegia develops rapidly the legs may at first be flaccid and the tendon-jerks absent. The appearance of spasticity in the course of a few weeks makes the diagnosis of acute necrotic myelitis unlikely. The cerebrospinal fluid also is useful in distinguishing the two diseases as, though there may be an increase of cells including a certain percentage of polymorphs in both diseases, the protein is not greatly raised in neuro-myelitis optica.

When acute compression of the spinal cord is due to epidural abscess or Pott's disease, rigidity, pain and tenderness localized to the affected region of the spine are common early symptoms. In these cases, as also in those of painless carcinomatous deposits in the spinal canal the cerebrospinal fluid may closely resemble that found in acute necrotic myelitis. The demonstration of a spinal subarachnoid block is the most valuable distinguishing feature between the cases of compression and those of myelitis.

Differential Diagnosis of Subacute Necrotic Myelitis.

Both amyotrophic lateral sclerosis and subacute combined degeneration may cause some difficulty in the early stages of the disease, but the development of sphincter disturbance and sensory changes will soon exclude the former, and the absence of dysæsthesiæ in the hands and the normal blood-count and gastric analysis the latter.

Chronic meningo-vascular syphilis affecting the lumbo-sacral cord has to be excluded, and in cases of chronic syphilitic myelitis with syringomyelia in which the Wassermann reaction is negative in the blood and the cerebrospinal fluid, this may be difficult. A case, proved by post-mortem examination to be of this type, was in the National Hospital under the case of Dr. Grainger Stewart in 1931 ; in this case the history and progress of the disease were practically the same as in subacute necrotic myelitis, the chief difference being the appearance of sensory impairment at practically the same time as motor function was affected. In this case there was a gradual ascent of the sensory level with pain involved earlier and to a greater extent than touch, a feature which Foix and Alajouanine stress as being almost pathognomonic of subacute necrotic myelitis. The cerebrospinal fluid contained 100 mgm. per cent. of protein and 1 cell per c.mm.; and the Wassermann reaction was negative in blood and cerebrospinal fluid. There was, however, evidence of subarachnoid block by the Queckenstedt test. The fact that the patient was known to have had an acute syphilitic meningitis some years before, and that his pupils reacted poorly to light, indicated the syphilitic nature of the lesion. The case described by Riser, Giraud and Planques (1937) as one of subacute necrotic encephalo-myelitis appears to us to be of this type.

The most difficult differential diagnosis, and the most important from the point of view of treatment, is that from extra- or intra-medullary tumours in the lumbo-sacral region of the cord. Clinically the differentiation may be practically impossible, as a slowly progressive course, associated with localized wasting, sphincter disturbance and sensory changes, occurs in both diseases. The two main differential points are the frequent occurrence of root pains and pain in the back in extra-medullary tumours, and the gradual ascent of the sensory level which is usual in cases of subacute necrotic myelitis and rare in cases of tumour. The presence of subarachnoid block at lumbar puncture will settle the diagnosis, since tumours at this level which are producing marked disturbance of function in the cord are invariably associated with some degree of spinal block. The albumin-cellular dissociation in the cerebrospinal fluid which has been stressed by Foix and Alajouanine has not been a feature in our cases, in neither of which did the protein exceed 100 mgm. per cent.

V.—DISCUSSION OF THE PATHOLOGICAL CHANGES.

Acute necrotic myelitis.—In Case 1 it appeared to us that the lesions in the cord were altogether explained by the changes in the small vessels. Every area of necrosis was associated with a small artery, the walls of which were so thickened that its lumen was almost if not completely obliterated. Why the grey matter was less affected than the white matter is not so easily explained. This may have been due to the relatively greater vascularity of the grey matter, and also to the fact that the most affected vessels were the small meningeal branches, whereas the arteries which entered the cord by the ventro-median fissure were only slightly involved. The type of degeneration in these vessels was that seen in syphilis and in some other subacute infective processes, e.g. tuberculosis, but there was no clinical or pathological evidence of either of these diseases. Nor is it clear why the vascular disease was limited to the lower segments of the spinal cord.

Of the previously published cases that which bears the closest relationship to this case is Juba's in which he emphasizes that the hyaline thickening was limited to the small vessels. In his case the large veins were also thickened, their walls consisting of loose concentric layers of fibrous tissue infiltrated with lymphocytes. In our case only one large vein was affected and that to a slight degree only; the infiltration which was seen round many seemed to be explained by the rapid degeneration of the tissues of the cord.

In our subacute cases (Nos. 2 and 3) the resemblance to the original cases of Foix and Alajouanine was very close but the lesions in the cord were not so frankly necrotic as in their cases. It is true that small patches of necrosis were seen in both, but the earlier stages of lacunar degeneration were much more in evidence. Nor was there as much degeneration of the neurones of the ventral horns in our cases as in theirs. This may have been due to the earlier stage at which our cases terminated. In Minea's case also there was little affection of the anterior horn cells, and although he uses the word "necrosis" to describe the degeneration, it is clear, both from the text and the illustrations, that he means what we have called "degeneration with mesodermal reaction." But the vascular changes in his case as in ours were almost exactly similar to those in the original cases and were remarkable if not unique. The sparing of the larger arteries was noteworthy in our cases. In the second case of Foix and Alajouanine they note that the veins were at least as much affected as the arteries but the latter appear to have been affected in both cases. In both the original cases and in our own there was no reduction in the lumen of the larger vessels, in spite of the great thickening of their walls. The degeneration appeared to be due rather to sclerosis of the small intramedullary vessels. This cannot have been caused by the thickening of the walls of the large veins, but must have been an independent process.

In both cases of Foix and Alajouanine and in our own there was evidence of pre-existing vascular disease. Their first case had had albuminuria five years before the onset of paraplegia, and their second case had had several attacks of lead colic. In our Case 2 there was a definite history of gout and he had suffered from auricular fibrillation for years. In our Case 3 the only history of vascular disease was phlebitis of the legs at about the same time as the onset of paraplegia, and he died from thrombosis of the renal vein which spread to the inferior vena cava. It is not, however, certain that the affection of the spinal vessels bore any relationship to pre-existing vascular condition which, in no case, was of an unusual form. If the disease of the small intra-medullary vessels were a part of a systemic vascular disease it might be expected to be more common in sufferers from severe arteriopathic conditions, whereas it appears to be extremely rare.

The possibility that it is a special form of toxi-infectious disease of the spinal cord has been suggested by Foix and Alajouanine for the subacute cases, and by several of those who have reported more acute cases. The peculiar course of the disease and its incidence on the grey matter of the lumbo-sacral enlargements suggest that it may be a clinico-pathological entity. But our cases at least gave the impression that the parenchymal lesions were altogether dependant on the disease of the vessels.

It is impossible to trace the pathogenesis of the disease farther than this, but we incline to the view that in this form of myelitis we have a peculiar form of degeneration of the small vessels of the spinal cord, associated in the more chronic cases with great thickening of the walls of the larger veins. The presence of early lesions in the latter in our acute case and in Juba's case indicates that this, although the most obvious pathological feature in the subacute cases, may be of later development than the changes in the small vessels of the cord.

[We should like to express our thanks to Drs. Gordon Holmes and C. P. Symonds for permission to publish their cases.]

VI.—SUMMARY.

One case of acute and two of subacute necrotic myelitis (Foix and Alajouanine) are described, and their clinical and pathological relationships to the previously published cases is discussed.

The clinical picture of progressive amyotrophic paraplegia, with dissociated sensory changes and loss of tendon reflexes and of sphincter control, is sufficiently characteristic, if taken in conjunction with the condition of the cerebrospinal fluid, to allow of clinical diagnosis.

The condition consists essentially of primary obliterative sclerosis of the small intra-medullary and meningeal vessels in the lower segments of

the spinal cord, and is associated with great thickening of the walls of the larger meningeal veins and sometimes also of the larger arteries.

The degeneration of the parenchyma of the spinal cord appears to be altogether secondary to the vascular lesion.

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SOME OBSERVATIONS ON CENTRAL PAIN.

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THE first description of the so-called thalamic syndrome was given by Dejerine and Roussy in 1906 and was elaborated by Roussy a year later.

Since that time many cases have been recorded that display the disorders of sensation composing this syndrome, and various explanations have been put forward to account for the phenomena met with. It has become apparent that the only essential feature of the thalamic syndrome is a disorder of sensation, and that the athetoid movements and ataxia described by Dejerine are not necessarily present. They depend on the extent to which the lesion involves structures in the immediate neighbourhood of the thalamus.

These disorders of sensation are not found in association with thalamic lesions only. They may occur with lesions of the brain-stem, of the spinal cord and even of the peripheral nerves. Moreover, the clinical findings do not differ in any material respect from those of the thalamic syndrome.

The term " spontaneous pain " has been much used in connection with this subject, especially in reference to the pain which *apparently* arises spontaneously in thalamic lesions. It is, however, doubtful whether this does in fact occur, as an intimate study of these cases suggests that the pain is usually excited by some external stimulus, be it only a draught from an open window or the contact of clothing with the surface of the body. Head and Holmes (1911), who originally pointed this out, put forward the suggestion that the pains associated with thalamic lesions are the result of interruption of cortico-thalamic fibres, the function of which is to inhibit the reaction of the thalamus to afferent impulses arriving at the thalamus. In order to account for apparently spontaneous pain occurring as a result of spinal lesions, it would be necessary on this hypothesis to assume the presence of a cortico-spinal tract, the function of which would be to inhibit sensory impulses in their passage through the grey matter of the spinal cord. It has not, up to the present time, been possible to prove the existence of such a pathway.

Kinnier Wilson (1927), who pointed out that pain does not occur in association with lesions of the cerebral cortex, put forward the suggestion that pain, when associated with lesions of lower levels of the central nervous system, resulted from the irritation of conducting nerve fibres. This suggestion had previously been supported by Spiller (1923). It is, however, difficult to conceive an irritative process continuing sometimes for many years with little or no change in function taking place, as judged by clinical evidence. This suggestion would appear to endow individual nerve fibres with the property of conducting impulses in a different manner, depending upon whether or not they are subject to irritation, a theory which finds little support from studies of the properties of nerve fibres.

Riddoch and Critchley (1937) and Riddoch (1938) also emphasize the probable existence of an inhibitory process active in the mechanism of sensation, and suggest that central pain occurs when this inhibition is defective. They also suggest that irritation may play a part in the production of central pain in those acute cases in which pain is a transient phenomenon. The same authors consider that the inhibition takes place at some point in the central nervous system distal to the thalamus.

Following indirectly upon the observations of Head (1905) on protopathic and epicritic sensibility, Foerster (1927) postulated the existence of two sensory systems: (1) the affective, for the quality, i.e. pleasantness or unpleasantness of sensation, and (2) perceptive or epicritic, for the analysis of sensation into warmth, coolness, touch, &c. Further, he has suggested that the affective qualities of sensations are conducted in the posterior columns of the spinal cord. The evidence for this suggestion is based largely on the results of stimulating the posterior columns of the spinal cord in man. It is difficult to understand what bearing the production of pain by such stimulation with an electric current can have in indicating the pathway of painful impulses under normal conditions. Neither is this suggestion confirmed by clinical findings. Holmes (1919) has recorded cases of gunshot wounds of the spinal cord associated with severe pain and over-reaction, in which there was clinical evidence of involvement of those modalities of sensation which are commonly assumed to be carried in the posterior columns of the spinal cord.

Nicolesco (1924) has drawn attention to the frequency with which lesions affecting the grey matter result in pain. Although this is suggestive, there is no evidence to show that the production of pain is an exclusive property of lesions of the grey matter, and the observation in itself is of little assistance in finding a reason for the occurrence of so-called central pain.

The essential feature in cases presenting pain as a symptom of lesions of the central nervous system is an over-reaction to stimuli capable of exciting affective reactions and sensations, that is, those sensations naturally endowed with pain or pleasure. It would seem, therefore, that the term "central pain" is a misleading one, and that the term ' dysæsthesia " is sufficiently explanatory and at the same time non-committal.

The hypothesis put forward in this paper is that the essential factor determining the appearance of dysæsthesiæ is the functional dissocation of two sensory pathways which are to some extent antagonistic, but which are mutually interdependent for the production of what is known as normal sensation.

Certain experimental and clinical observations are brought forward and discussed.

EXPERIMENTAL OBSERVATIONS ON THE PERIPHERAL NERVES.

Head, in 1905, was the first to suggest, as a result of observations made upon himself, the possibility of a double function in afferent nerves, and, although many observers have failed to substantiate his observations and conclusions, the terms protopathic and epicritic are useful in emphasizing the existence of dissociation of sensation in the peripheral nerves. It is not possible, however, to interpret Head's findings on a strictly anatomical basis owing to the marked degree of overlap that exists between the fields of adjacent peripheral sensory nerves, and it is possible that the protopathic sensibility observed by Head was the property of certain types of fibres, the nature of which will be discussed later, which overlapped from adjacent areas.

The observations made upon protopathic sensibility showed that the response to stimulation closely resembled the response obtained in the thalamic type of syndrome. The response was excessive once the raised threshold was overcome, and the resulting sensation radiated over a wide area. Also the majority of stimuli that could be perceived at all had an unpleasant quality.

The work of Gasser (1934 and 1937), of Erlanger and Gasser (1930), of Lewis and Pochin (1937 and 1938), and of Ranson (1915) are of great interest and seem to have an important application to this subject. Ranson put forward the suggestion that "protopathic sensibility" is conducted by the unmyelinated fibres in the peripheral nerves. Ranson and Billingsley (1916) produced convincing evidence from experiments on cats that painful impulses are largely carried by the fine non-medullated fibres which lie in the lateral part of the posterior nerve roots and end in Lissauer's tract. Further, Ranson and Davenport (1931) showed that the non-medullated fibres outnumber the medullated fibres in the peripheral nerves of the cat after time has been allowed for degeneration of the sympathetic fibres.

The work of Lewis and Pochin and of Erlanger and Gasser has thrown some light on the possible functions of the different types of nerve fibres in the peripheral nerves. Erlanger and Gasser (1930), by an investigation of action potentials, were able to demonstrate that the fibres fell into three groups: A, B, and C. The A fibres are large and medullated and are the fastest conductors of impulses. The B fibres conduct more slowly and are thought to correspond with the finer medullated fibres, and finally the C group, which are the slowest conductors, probably consist of fine non-medullated fibres.

These investigations were carried further by Clark, Hughes and Gasser (1935), who investigated the effects of asphyxia on the conduction of impulses in the peripheral nerves. From the temporal order in which the various modalities of sensation were lost they were able to conclude that crude unlocalized pain is carried in the C group of fibres, that is, the slowly conducting non-medullated fibres.

The effect of asphyxia on the sensory functions of peripheral nerves has been further investigated by Lewis and Pochin (1938). Asphyxia was produced either by a pressure cuff round the arm, or by a specially designed clamp which compressed the nerve without introducing the factor of vascular occlusion. They were thus able to conclude that the results obtained were due to compression of the nerve only and were not due to circulatory disturbance. It was found that touch, perception of cold, perception of warmth, and rapidly conducted painful impulses were impaired almost simultaneously, while so-called "slowly conducted pain" was affected later, and the defect was preceded by a period during which the response to painful stimuli was exaggerated. It was the second pain which was exaggerated and the pain evolved persisted longer than under normal conditions; in this stage even scraping the fingers or pressing on the nails was painful and unpleasant.

The work of Lewis and Pochin (1937) on the double response of the skin to a single stimulus is particularly significant. They were able to show that a single stimulus, such as a prick applied to the skin, produces two definite and separate sensations, separated by an interval, the length of which they were able accurately to record. The initial perception of sharpness is almost instantaneous and is followed after an interval measurable in seconds by a more prolonged sensation of pain.

Putting these observations together, it seems reasonable to assume that in the peripheral nervous system painful stimuli, at least, travel in two distinct sets of nerve fibres, through the rapidly conducting large medullated fibres, which transmit the "first pain," and through the small non-medullated fibres, which transmit the "second pain." It appears possible to apply this hypothesis to impulses created by extremes of heat and cold.

It is a common observation in everyday life that when part of a limb is placed in excessively hot water or comes into contact with an unduly hot object, there is immediate withdrawal of the limb. After an appreciable interval (about one second in the hand) there is a second and more intense sensation of heat, not confined to the area immersed, but radiating proximally. This second sensation is more painful than the first and is of considerably greater duration. It has the same unpleasant quality that is found in patients with pain resulting from central lesions. This form of response is much more noticeable if the limb is previously cooled; then water at a temperature normally quite bearable or even pleasant seems intensely and unpleasantly hot. Following on this initial sensation there is a still more severe or unpleasant sensation of burning heat comparable to the second pain, which may be very prominent.

In order to determine whether or not this latter is a result of local cooling of the skin and nerve endings, it was decided to make a personal experiment. The left ulnar nerve was cooled locally at the elbow by water at 3° C. for one hour. At the end of forty-five minutes it was found that there was complete loss of thermal discrimination over the ulnar two fingers and ulnar border of the hand. Hot and cold objects were described alike as being hot. This "hot sensation" had a very unpleasant and intense burning quality and corresponded very closely with the sensation produced by the immersion of an unduly cold limb in hot water. There was a delay of about one second in appreciating the sensation. In this experiment there was little or no excessive reaction to pin-prick; there was merely a raising of the threshold.

These observations are compatible with those made by Gasser *et al.* and Lewis and Pochin on the results of asphyxia of a peripheral nerve. In each case a double response is observed, and in each case it is possible experimentally to dissociate the two responses. In the absence of the first response the sensation produced by the second response is exaggerated and has a particularly unpleasant quality.

It can therefore be stated with reasonable certainty that in the peripheral nerves, painful impulses are transmitted by two anatomically independent but functionally related pathways, and that the distinguishing features of these two pathways are the size of the fibres concerned and the rate of conduction of impulses travelling thereby. Further, it appears that one conducting system is capable of exercising a modifying influence over the other. It is suggested that this is concerned with an inhibitory mechanism within the central nervous system.

Reviewing Head's observations, it is probable that the type of sensibility that he noticed on the ninth day following nerve section and termed protopathic, was due to stimulation of unmyelinated, slowly conducting fibres arising from intact adjacent nerves. It has been demonstrated that the distribution and ramifications of this type of fibre covers a wider area than the corresponding large medullated fibres. This statement is, however, open to criticism, as the exact distribution of these unmyelinated fibres has not been demonstrated.

The question now arises whether it is possible to apply the hypothesis of a double conducting system in the peripheral nervous system to the central nervous system. Are there, in the central nervous system, two anatomically distinct pathways for the transmission of painful and thermal sensations which conduct impulses at different speeds?

If this could be shown to be the case considerable light would be thrown on the mechanism of production of the excessive response to peripheral stimulation found in certain cases with central lesions.

In order to test this hypothesis four cases have been studied, in each of which this excessive response was present. The lesion in one case was in the lower cervical region of the spinal cord; in the remaining three it was situated in the ponto-bulbar region. The fourth case was not examined personally, but is included in this paper on account of its similarity to the other cases described.

Each case showed a very striking uniformity in the type of dysæsthesia present, and in its mode of production. The findings are most conveniently examined when grouped together under appropriate headings. Full details of the histories and findings are to be found at the end of this paper.

(1) *"Spontaneous" pain.*—Each patient complained of a constant discomfort over the affected area of the body. The description given varied from a "constant dull ache" to "a feeling like neuralgia," "an uncomfortable heavy feeling" or "like electricity." In two of the cases the pain was so severe as to require the administration of opiates.

Careful questioning elicited the fact that the pain was not truly spontaneous it could be shown that in each case it was the response to some environmental condition such as the presence of the bedclothes in contact with the skin or the temperature of the surrounding atmosphere. The pain or discomfort was almost constantly present, but was considerably modified by external conditions. Sudden movement or changes in temperature, lying on the affected side, in fact, any sudden change in environmental conditions tended to aggravate the discomfort. Further features of this "spontaneous" pain were its widespread distribution, the lack of any exact localization, and the absence of any one spot of maximal intensity.

(2) *Pin-prick.*—The response in all four cases was similar. The stimulus caused very excessive pain which seemed to radiate over a very wide area and which frequently had a very nauseating character. Localization of the stimulus was faulty, and the exact site of reference of the pain was indefinite and difficult to determine. A very significant fact in the first three cases was the presence of delay in the appreciation of pain; this was constant and bore no relation to the intensity of the stimulus. The response to pin-prick was therefore strikingly similar to that obtained in a limb the slow conducting nerve fibres of which have been isolated by experimental asphyxia of the nerve trunks.

In only one case (No. 4) was there any marked raising of the threshold to pain. In the remaining three cases the threshold was variable and differed only very slightly from the normal.

(3) *Thermal sensibility.*—In Cases 1, 2 and 3 very similar responses were obtained. Cold objects caused intense pain, the character of which resembled closely that caused by pin-prick, to which was added a sensation of coldness of an abnormal and very unpleasant nature. The intensity of the response was much increased by using a massive stimulus, such as a jug of cold water as opposed to a test-tube. In addition there was delay in appreciating the stimulus, that is, there was a delay between the contact of the test object with the skin and the appreciation of the sensation of painful coldness referred to above. This delay was more variable than that found to pin-prick; it was always greater than one second and, using a small test object, it was found to amount to four seconds in one of the cases.

In Case 4 only was there no over-reaction to heat or cold, but here there was complete loss of perception of temperature over the affected area.

In describing the response to thermal stimulation it is interesting to quote the case of Admiral Broke, referred to by Weir Mitchell (1897). Following an unspecified lesion of the central nervous system the patient described "a sense of extreme cold in my leg and foot and left hand, so that I could not sleep in comfort without a worsted glove and worsted stocking . . . the sense of cold appeared to be internally upon the coating of the bones . . . and yet the skin over the whole left side of my body was affected with a singular numbness to the touch." The abnormalities of sensation were further described; "the left side requires four coatings of stout flannel, which are augmented as the thermometer descends . . to prevent a painful sensation of cold. . . . When exposed to a breeze, or in moving against the air, one or even two oilskin coverings are necessary, in addition, to prevent a sensation of piercing cold driving through the whole frame." It is interesting to note that the same author refers to two similar cases resulting from vascular lesions which he thought to involve the thalamus. Weir Mitchell was, therefore, probably the first to describe the thalamic syndrome, and he also recognized that the pains were not truly spontaneous.

The symptoms quoted above bear a strong resemblance to those of the cases here referred to.

In general it may be said that in these cases the perception of light touch was unimpaired and in one case only was there any impairment of those modalities of sensation (postural sensation, perception of passive movement and vibration) which are said to travel in the posterior columns of the spinal cord; in this case (No. 2) the impairment was minimal.

The presenting features of these cases are therefore that in each case there was an area of the body throughout which certain stimuli were abnormally appreciated. The abnormality consisted principally of an excessive reaction and faulty localization, together with delay in the appreciation of the stimulus. A further point of importance which arises is that with one exception (Case 4) little or no raising of the threshold to stimuli could be detected by ordinary clinical methods. This fact seems to imply that the total amount of damage to the pathways conducting afferent impulses from the affected area was not very great, and it is significant that in Case 4, in which there was complete loss of thermal discrimination, there was no over-reaction to hot or cold objects. This observation is in keeping with the majority of accounts of cases presenting dysæsthesia resulting from central lesions; the dysæsthesia is not present in areas in which the loss of cutaneous sensibility is complete. This may have some bearing on the point raised by Garcin (1937) that lesions in a given part of the central nervous system produce very similar clinical pictures, but may differ in that in one case over-reaction to cutaneous stimulation may be present, in another absent. It is suggested here that the degree of damage to the sensory conducting pathways bears a definite relation to the presence of over-reaction. The greater the damage, the less the likelihood of over-reaction occurring.

It is not inappropriate at this point to refer to the condition known as causalgia on account of the similarity of certain symptoms to those that may result from central lesions.

Causalgia is characterized by severe and persistent pain following peripheral nerve injury, and it is commonly found that the degree of actual sensory impairment is slight or even non-existent. The pain in this condition is excited by peripheral factors; either by touch, change in temperature, pin-prick, movement or pressure. In addition, the pain is widespread, often has a nauseating character, and appears to radiate through both superficial and deep structures. It seems possible, therefore, that causalgia may depend for its causation on factors similar to those concerned in the production of pain from central lesions.

Discussion.

An analysis of the work of Gasser *et al.*, and of Lewis *et al.*, referred to above, and of the clinical features of cases presenting dysæsthesia with central lesions, shows that there are certain features common to both.

Experimental lesions of the peripheral nerves produce delay in the perception of pain, together with over-reaction and abnormal perceptions. This appears to resemble very closely the clinical findings in cases presenting so-called central pain. In both, exaggeration of sensations evoked and delay in perception are present. Again, it is emphasized that the experimental lesions producing these phenomena are such as to cause *partial* interference with the normal transmission of afferent impulses ; there is loss of the " first pain " together with a defect in the conduction of tactile and thermal stimuli. Further, it is known that the fibres subserving delayed pain in the peripheral nerves are fine unmyelinated ones, and possibly some of the smallest myelinated fibres. The thesis put forward here is that a similar double pathway for the conduction of afferent impulses exists in the central nervous system, and extends from the spinal cord to the thalamus.

On the basis of this hypothesis it is possible to explain the phenomena of so-called central pain by a disturbance of a central inhibitory process. This paper is not concerned with the theories of the mechanism of production of the central inhibitory state, which has been investigated by physiologists (Sherrington and others) chiefly in the motor aspects of nervous activity. Excitation of an axon results in a period of subnormal response in the axon and at the synapses and a raised threshold is produced which renders the neurons refractory, for a time, to further impulses which may arrive. Gasser (1937) has, however, assumed the existence of a similar function on the afferent side. He has drawn attention to the possible relationship between the different rates of conduction in peripheral nerve trunks and a central inhibitory process. He states: "it is quite possible that the function of the impulses which run ahead of the others is to adjust the excitability of the synapses in preparation for the arrival of later impulses." Impulses travelling in the large, fast-conducting fibres reach the central nervous system and act upon certain receptors and render them relatively refractory to the second set of impulses excited by the same stimulus, which arrive later by the slowly conducting fibres.

The question then arises of the site of this inhibition. Riddoch (1938) stresses the possibility of modification of afferent impulses at the various synapses in the afferent pathways.

Direct experimental proof on the human subject is lacking, and evidence from animal experiments must necessarily be inconclusive when sensation is concerned. In order to state definitely that there are two pathways for the conduction of painful impulses in the spinal cord, it would be necessary to determine accurately the time relations of the various afferent pathways, and the various fibres of different sizes within them. There are two places where inhibition would be most likely to take place; at the posterior horns of the grey matter, or in the thalamus. A fact in favour of the possible inhibition at the thalamic level is the occurrence of dysæsthesia with thalamic lesions. Therapeutic cordotomy, on the other hand, at least shows that all the fibres concerned in conveying impulses of pain and temperature are grouped together in the antero-lateral part of the spinal cord. This fact is against the existence of a separate pathway in the posterior columns for the affective component of sensation, as suggested by Foerster. If inhibition takes place in the posterior horns and the impulses crossing to the opposite antero-lateral columns are, as it were, already modified for recepttion by the higher centres, it is difficult to understand how lesions involving the central grey matter can give rise to pain and over-reaction referred widely below the corresponding level. It therefore seems probable that the fibres in the antero-lateral columns maintain the arrangement that holds for the peripheral nerves, that is, both fast and slowly conducting fibres. On this hypothesis the response to impulses with a high affective quality may be inhibited at the thalamic level by more rapidly travelling impulses excited by the same stimulus. Under normal conditions the reaction to such affective stimuli is modified or controlled by such a mechanism. If, however, the rapidly conducted inhibitory impulses are blocked or modified, the response to the stimulus is naturally excessive, and shows itself by the exaggeration of the sensation of pain and the greater response in the withdrawal of the stimulated part.

In other words, on this assumption that there is a double pathway for afferent impulses exciting pain, the clinical phenomena of "central pain" can be interpreted as the result of interruption of the "fast-conducting" fibres in the spinal cord and brain-stem by a lesion which leaves intact or relatively intact the "slow-conducting" fibres which are normally inhibited by them.

Little can be said about the relative sizes of the fibres in the afferent pathways of the spinal cord. It is known, however, that those fibres of the spino-thalamic tracts, the course of which is uninterrupted to the thalamus, are uniformly small and few in number. It is probable that other and larger fibres which conduct rapidly, may reach the thalamus indirectly by a series of relays.

This hypothesis of a spino-thalamic inhibition of afferent impulses is the opposite of that of Head and Holmes, who postulated a cortico-thalamic inhibition. There is no reason why a spino-thalamic and a cortico-thalamic inhibitory process should not both play a part in the control of afferent impulses.

SUMMARY.

An attempt has been made to correlate certain features of pain resulting from central lesions and observations on the consequences of experimental disturbances of the peripheral nerves. Attention is drawn to the occurrence in both of over-reaction to certain stimuli, irradiation, and delay in the perception of pain.

It is suggested that the double conducting pathway in the peripheral nervous system described by Gasser *et al.* exists also in the central nervous system, and that the pathways differ in the rate at which impulses are conducted by them. It is further suggested that, in normal circumstances, the rapidly conducted impulses produce a relatively refractory state centrally, which has a modifying effect on the impulses conducted slowly

APPENDIX.

CASE HISTORIES.

Case 1. — K. T., female, aged 34. Admitted to the National Hospital January 15, 1939, under the care of Dr. Gordon Holmes.

Complaint.—Progressive paralysis of the limbs for twenty-four hours. On attempting to get out of bed on the morning before admission, she noticed an uncomfortable strained sensation on the left side of the thorax that seemed to cover the left side from vertebræ to the sternum. In the course of a few minutes this sensation became one of intense pain. She then felt that her lower limbs and trunk were becoming tight, particularly on the left side. At the same time she very rapidly lost the use of both legs, and her left arm and hand became weak. The left side of the body felt numb and sore up to, and including, the left hand. There was also some tingling in the left foot. She developed retention of urine and fæces at the onset of the paralysis. There was some pain in the left side of the chest, aggravated by breathing or movement. The tight sensation in the chest had occurred once before, three years before the present attack, and was sufficiently severe to prevent her working. There had, at that time, been no paralysis of the limbs.

Examination.—There was a left-sided Horner's syndrome. The skin of the left side of the face was dry and contrasted markedly with the opposite side which sweated profusely. The left palpebral fissure was narrowed, and the left pupil was smaller than the right. Both pupils responded normally to light and convergence. The remaining cranial nerves showed no abnormality. There was great resistance to any movement of the neck, particularly to flexion, with tenderness over the 7th cervical spine.

Motor system.—Arms: There was weakness of all the intrinsic muscles of the left hand, together with some weakness of flexion of the left wrist. The left arm was hypotonic. There was no wasting and co-ordination was normal.

Trunk: There was impaired movement of the left side of the chest in respiration. On raising the head there was deviation of the umbilicus to the right.

Legs: There was an almost complete flaccid paralysis of both lower limbs The only movements present were very weak flexion and extension of the right foot and weak eversion of the right leg. There was apparently extreme tenderness of the left calf muscles (*see under Sensation*).

Reflexes.—The left triceps-jerk was diminished. The abdominal reflexes, knee and ankle jerks were absent. The plantar responses were flexor. In the course of the next month power returned fully in the right leg and partially in the left. Some wasting appeared in the intrinsic muscles of the left hand. Both plantar responses became extensor and the reflexes in the lower limbs became brisk. She was able to walk with the aid of a stick. Bladder function had partially returned at the end of three weeks, but some precipitance persisted.

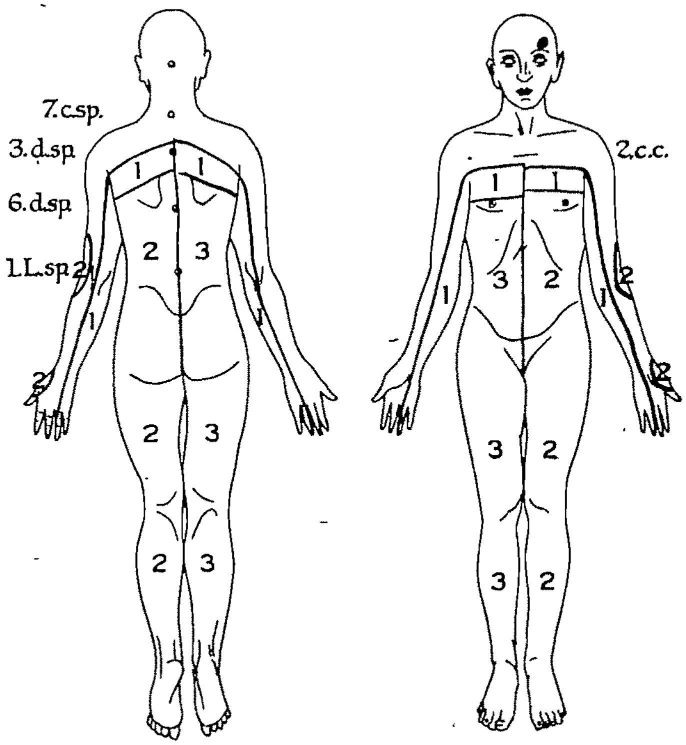
Sensation.—(The findings with regard to sensation remained practically unaltered throughout the patient's stay in hospital. The findings here recorded are condensed from a number of different examinations in the course of six weeks.)

(1) *"Spontaneous" pain*: On the day following admission the patient complained of severe left-sided abdominal pain, radiating upwards to the chest, and downwards in the left leg. The pain was so severe as to resemble an intra-abdominal catastrophe. Examination showed no evidence of this. It was described as an aching, boring or gnawing pain, greatly aggravated by coughing or movement, and somewhat relieved by lifting the bedclothes away from the skin and by moderate warmth indirectly applied. This pain only persisted for forty-eight hours ; it then gradually improved Throughout the illness there was an almost constant dull ache over the left elbow and in the left scapular region. At first this dull aching affected the whole of the left side of the body. After a few days it was only present in the left leg and trunk when some sudden movement was made. (In order to save space certain areas of the body have been numbered on the chart and reference is made to these numbers in the text.)

(2) *Light touch (fine wool)*: Over the area marked (1) on the chart there was a minimal impairment of the perception of light touch. Over the area marked (2) the perception of light touch was abnormal in character. The contact of the wool with the skin had a distinctly uncomfortable burning quality, and the area over which the stimulus was perceived was much larger than normal. Over area (3) perception of light touch was normal.

(3) *Tickling the skin with wool*: Over area (1) the quality of the response was

normal, but there was a quantitative impairment. Over area (2) the sensation produced was unpleasant and nauseating, and was described as resembling the sensation resulting from scraping coarse sandpaper with the finger-nails. Over area (3) there was a diminished quantitative response. Qualitatively the sensation produced was described as "pleasant," "soothing," "comforting." "It sends a pleasant feeling up my spine." Tickling with the tips of the fingers (i.e. a more massive stimulus) produced the same subjective response as tickling with wool, but to a greater degree.



(4) *Scratching the skin with the fingers*: Over area (1) there was a normal qualitative but diminished quantitative response. Over area (2) a very intensely unpleasant sensation was produced. It was described as being "like scraping a raw piece of skin." There was radiation of the response over a much larger area than that stimulated. Over area (3) the response was not definitely abnormal.

(5) *Pin-prick*: There was no great difference in the quality of response produced by light or by heavy application of the pin. The difference was only a matter of degree. Over area (1) there was diminished perception of pin-prick, heavy and light. Over area (2) there was no raising of the threshold to pin-prick; there was, however, a very marked delay in the perception of the pain. This amounted to about one second in the upper trunk and rather over two seconds on the left leg. When asked to compare the response on the left leg with that on a normal area

(neck or radial border of right hand) the patient was able to recognize (without direct questioning) the double nature of the response over the normal areas. Over the affected area (2) the initial sharpness of the pain was missing, and there was a delay between the application of the stimulus and the perception of pain. This was borne out by the delay in withdrawing the limb from the stimulus. In addition to the above, there was faulty localization of the stimulus. She was unable to point with a greater accuracy than within several inches to the place where the stimulus had been applied. (This she could do accurately over normal areas) The character of the response to pricking was one of intense pain. It was described as "burning," "sickly," "covering an area" and "sending a cold shiver right through my body." "It was like stabbing a cut." Over area (3) a pin could be recognized as such, but did not feel painfully sharp even with a heavy stimulus. The response was neither pleasant nor unpleasant. The chief abnormality lay therefore in area (2) which showed: *a*) Delay; (*b*) over-reaction; (*c*) irradiation; (*d*) faulty localization; (*e*) a normal threshold.

(6) *Drawing a pin across the skin*: Over area (1) this was perceived as touch only. Over area (2) the response was similar in character to pin-prick—"like a hot match being dragged along my skin." Over area (3) the response was subnormal in degree and was pleasant in quality. Like tickling, it was "soothing and rather exciting."

(7) *Heat*: (*a*) Using a stimulus of small dimensions (temperature of test object just pleasantly bearable on normal skin). Over area (1) it felt just warm; it was neither pleasant nor unpleasant, and the quantitative response was subnormal. Over area (2) there was delay similar to that observed with pin-prick. The sensation produced was one of intensely painful heat which covered a wide area of the body. "It was like putting a burnt hand into hot water." Over area (3) the test object felt "just warm"; it had a pleasant and soothing quality and she stated that she felt she would like it to be warmer. Everything in contact with area (3) felt warm irrespective of its actual temperature, and the degree of warmth was always the same. (*b*) Using a massive stimulus: (rubber hot-water bottle.) The responses over areas (1) and (3) were the same. Over area (2) the sensation produced was quite unbearable, and seemed to spread over the whole of the left side of the body.

(8) *Cold*: Over area (1) there was defective perception of cold. Over area (2) there was delay in appreciating the stimulus, followed by great over-reaction and irradiation. The sensation was one of unbearably painful cold. Over area (3) the cold object felt just warm, and was indistinguishable from the warm object. The patient described how, on getting into a warm bath for the first time after the onset of symptoms, she first put in her right foot, and said "this is not hot enough." On being told that it was really very hot, she ventured to immerse her left foot To her surprise she was obliged immediately to remove her left foot from the water, the heat was so intensely painful. When eventually a compromise had been reached as to the temperature of the bath, she described how she enjoyed her bath with the right side of her body, and felt nothing but discomfort on the left.

(9) There was a very slight impairment of tactile localization over area (2). This was not detectable when the lightest possible stimulus was used, but became noticeable when the stimulus was sufficiently strong to cause irradiation

(10) Perception of vibration, position, passive movement, and compasses was normal everywhere.

There was no astereognosis.

Diagnosis.—In view of the fact that the cerebrospinal fluid contained blood on three consecutive occasions during the first week, it was assumed that hæmorrhage was taking place from a vascular abnormality on the surface of the spinal cord in the lower cervical region. Progress was good and on leaving hospital seven weeks after the onset of symptoms the patient was walking well. She had still, however, a considerable amount of pain and aching in her left side. On discharge, there was little or no change in the sensory findings.

Comment.—This case was one of an acute lesion in the lower cervical region of the spinal cord on the left side. There was a modified Brown-Séquard syndrome, with over-reaction on the side of the lesion. In view of the persistence of the extensor plantar response on the right, it is reasonable to suppose some damage to the right side of the spinal cord, and that the antero-lateral column on the right was partially involved. It is significant that in area (2) there was practically no change in the threshold to stimuli.

Case 2.—H. B., male, aged 38. Admitted to the National Hospital October 13, 1936, under the care of Dr. Gordon Holmes.

Complaints.—(1) Numbness, tingling and discomfort of the right side of the body for twenty-two days ; (2) drooping of the left side of the face for seven days ; (3) dysphagia and dysarthria for seven days ; (4) a tendency to fall to the right for seven days ; (5) inability to look to the left for three days ; (6) diplopia on looking to the right for three days.

Until twenty-two days before admission to Hospital he had been quite well. The first symptom was noticed on getting into a hot bath. He noticed a very unpleasant tingling in his right leg from the toes to the hip. He was only able to continue his bath by keeping his right leg out of the water. During the following week the right leg became numb, and walking caused an uncomfortable sensation in the right foot. By the end of the first week of his illness the whole of the right side of his body felt numb, including the face. At the end of the second week of his illness several new symptoms appeared within the course of one day. The first was a difficulty in swallowing and articulation. This was probably due largely to a weakness of the left side of the face which occurred at the same time. Three days before admission double vision was noticed on looking to the right. The false image was above and to the right of the true. At the same time there was inability to turn the eyes to the left. On sitting up in bed there was a tendency to fall to the right, unaccompanied by any vertigo, but with a feeling of being forcibly pulled over to the right. There was no headache, no visual disturbance, no weakness of the limbs or sphincter disturbance. Family and past histories were negative.

Examination.—The patient was mentally normal. There was a slurring dysarthria, but no loss of words or lack of comprehension. The first and second cranial nerves were normal. The pupils were small, the left being smaller than the right. They were irregular, and reacted rather sluggishly to light and convergence.

Ocular movements.—Both eyes could be moved upwards, downwards, and to the right conjugately, but on being told to look to the left there was failure to move either eye. The right eye was adducted normally on convergence. With the eyes fixed on an object and the head rotated, it was still impossible to obtain conjugate movement to the left, showing that the interference with conjugate ocular movement was at a nuclear level. There was also weakness of abduction of the right eye, producing a homonymous diplopia. There was nystagmus on looking to the right, independent of fixation of vision. It was moderately coarse with slow phase toward the mid-line and a more rapid outward movement. There was no ptosis.

There was complete paralysis of the masseter and temporalis on the left side. There was impairment of perception of pin-prick over the first division of the 5th nerve on the left side. The changes in sensation on the right side of the face were identical with those on the right side of the remainder of the body, and are described later. There was a complete paralysis of the left side of the face, with impairment of sense of taste over the anterior two-thirds of the tongue on the left. The left palate reflex was absent, and the palate deviated to the right. The right vocal cord moved better than the left. The 11th and 12th cranial nerves were normal. Power in the limbs was normal and equal on the two sides, but there was some inco-ordination of cerebellar type in the upper and lower limbs on the left side. Tone was a little increased in the right leg. There was increase in the tendon reflexes on the right, with a right-sided extensor plantar response. The abdominal reflexes were absent.

Sensation.—(Sensation was entirely normal on the left side, and the following refers to the right side of the body, including the face.)

(1) "*Spontaneous*": The patient complained of a constant discomfort on the whole of the right side of his body which varied from time to time and seemed to be associated with environmental conditions. A draught from an open window, or a sudden impact on the bed caused considerable increase in the discomfort. The discomfort consisted of a gnawing, aching feeling, somewhat relieved by heat.

(2) *Light touch* (*cotton-wool*): Light touch was normally perceived throughout, with very occasional mistakes. When the touch was not perceived there was a reflex contraction of muscles in the neighbourhood. The character of the sensation was abnormal. At times a tingling was produced; at times burning. It was always unpleasant and was resented. Tickling the skin with cotton-wool produced a very unpleasant sensation as of insects crawling over the skin.

(3) *Pin-prick*: Throughout the right side a very abnormal response was obtained. The threshold to pin-prick was a little raised, but not markedly so. There was very marked irradiation of the sensation. "It covers an area"; "like an electric shock." Delay in the perception of the stimulus was present and was greatest on the leg. The duration of the sensation was considerably longer than normal. There was some impairment of localization of painful stimuli.

(4) *Thermal sensibility*: There was impairment in the ability to distinguish small differences in temperature on the right side, but larger differences were correctly recognized. The character of the response was abnormal, the abnormality being more marked to cold than to heat. Application of a cold object produced a very painful sensation of cold which seemed to come from a much larger area than that actually stimulated. There was delay in withdrawing the leg from the stimulus. Heat was not painful, but had not the normally pleasant quality which the patient observed on the left side. The abnormality of the response was even more noticeable using massive hot and cold stimuli. The latter were quite unbearably painful.

(5) There was a little impairment of perception of vibration on the right side, and the character of the sensation was abnormal "like a dentist's drill."

(6) Sense of position, passive movement, and stereognosis were not quite so accurate on the right as on the left side. There was a minimal impairment of two point discrimination in the right hand. The patient's gait could not be tested, but on sitting up in bed he fell to the right. No abnormality was detected in the cardiovascular, respiratory or genito-urinary systems.

Lumbar puncture was performed eight weeks later and showed no manometric abnormality. The fluid contained 10 mononuclear cells per c.mm. The total protein was 0·12 mgm. per cent. Nonne-Apelt and Pandy tests were negative. The Lange curve showed no change and the Wassermann reaction was negative. The patient made a steady recovery, and examination two years from the onset showed almost complete recovery of function in the affected cranial nerves, except for a little impairment of conjugate ocular movement to the left side and a slight residual left facial weakness. The motor system was entirely normal. Investigation of sensory functions showed that the initial findings still persisted, but were very much less marked. Examination three years from the onset showed still greater recovery, and the abnormalities of sensation were only just detectable. Pin-prick felt rather sharper on the right than on the left. There was no longer any delay.

Diagnosis.—The diagnosis of this case remained in doubt. It is possible that the condition was due to the thrombosis of the left posterior inferior cerebellar artery, but in the absence of any obvious cardiovascular disease the possibility of disseminated sclerosis could not be ruled out.

Comment.—This case showed abnormality in the perception of afferent impulses over a very wide area. The principal points were the absence of any great impairment of sensation, with marked over-reaction, and delay in the perception of pain.

Case 3.—S. R., male, aged 37. Admitted to the National Hospital September 22, 1938, under the care of Dr. Denis Brinton.

Complaints.—(1) Giddiness for twenty-four weeks; (2) vomiting for twenty-two weeks; (3) a tendency to walk to the left for twenty-two weeks; (4) crookedness of the face for five weeks; (5) dysphagia and hoarseness for five weeks; (6) an uncomfortable feeling in the right leg and right side of the trunk for five weeks.

The patient was well until six months before admission to hospital. He then quite suddenly noticed that bending down made him feel giddy. Objects seemed to rotate round him—he was uncertain in what direction. A few days later this giddiness became permanent, and he developed a tendency to fall to his left side. A fortnight later he developed early morning vomiting It was not definitely associated with the giddiness and there was no headache. He remained in this state until six weeks before admission, when the vomiting and vertigo gradually ceased. Five weeks before admission a number of new symptoms appeared within the course of about twenty-four hours. These were: drooping of the left side of his face, hoarseness of his voice, difficulty in swallowing, with regurgitation of fluids through his nose, and abnormal sensations in his right leg. He described the sensation in his leg as a "constant nagging toothache." It was present most of the day, but tended to get worse in sudden very sharp exacerbations. The pain at these times was not sharp but very unpleasant, and caused him to move his leg about continually. He also found that sensation over the rest of the right side of his body was abnormal. Anything touching his right side felt "unnatural." The sensation seemed to spread over a much larger area than was normal. This abnormality was present over the whole of the right side including the face. There had been no impairment of vision, but there had been some difficulty in looking to the left during his illness, and attempts to do so produced vertigo. There had been a severe cough with much sputum for three months before admission.

Examination.—The first and second cranial nerves were normal. The right pupil was larger than the left. The right eye was not adducted well on convergence. There was failure to move the eyes conjugately to the left beyond the mid-line, nor could movement to the left be obtained by rotating the head with the eyes fixed on a stationary object. The left eye could not be abducted when the right eye was covered. There was no diplopia. There was a coarse horizontal nystagmus on looking to the right; it was diminished but did not cease if fixation was prevented. The left corneal reflex was absent and it was impaired on the right. There was paralysis of the muscles of mastication on the left side. There was impairment of sensibility to pin-prick over all three divisions of the left 5th nerve. There was abnormal sensibility over the first two divisions on the right side which corresponded to the abnormality found on the trunk and limbs There was complete paralysis of the left side of the face, with hyperacusis in the left ear. The palate deviated to the right on phonation. The left vocal cord moved poorly. Power and tone in the limbs were normal. There was inco-ordination of cerebellar type in the left arm and leg. The abdominal reflexes were absent on the right side and the right plantar response was doubtfully extensor.

Sensation.—(The following description applies to the whole of the right side of the trunk, the right arm and leg, and the first two divisions of the right 5th nerve.)

(1) "*Spontaneous*": There was a constant "toothache-like" feeling in the right leg, which caused the patient constantly to move the leg about. It was aggravated by the presence of the bedclothes, or putting the foot to the ground.

(2) *Light touch* (*cotton-wool*): Light touch was everywhere appreciated at a normal threshold. On the right side it caused a sensation of irritation over an area wider than that actually stimulated. The sensation seemed to have a longer duration than normal.

(3) *Stroking or scratching the skin*: This caused a very unpleasant sensation as of rubbing a bruise beneath the skin, and was perceived over a very wide area. This response was most marked on the palms of the hands, the soles of the feet, and the abdomen.

(4) *Pin-prick*: (*a*) On the face. The threshold of pain sensation was normal but the character of the sensation was abnormal. The patient described "waves of feeling' radiating from the stimulated spot, found it very unpleasant "like an electric shock." No delay could be detected.

(*b*) Over the remainder of the right side. Here the threshold was a little raised. A light pin-prick was perceived only as very light touch. Heavier stimulation caused a very unpleasant painful sensation which radiated concentrically on the trunk and proximally on the limbs. The sensation was described not as ordinary sharpness, but a 'horrible gnawing sensation." There was delay in perception of the stimulus and the duration of the sensation was prolonged.

(5) *Thermal sensibility*: The ability to discriminate between fine grades of temperature was impaired on the right side, including the face. This defect was more marked than in Case 2. A test tube of cold water produced a sensation of painful coldness radiating over a larger area than that stimulated, but not radiating to the same extent as pin-prick. A warm test tube was more normally appreciated, but had a slightly unpleasant quality. Massive hot and cold stimuli were more effective in demonstrating the abnormality. There was delay in the perception of thermal stimuli.

(6) *Vibration*: This caused an unpleasant form of tingling radiating from the area stimulated.

(7) Perception of passive movement, two-point discrimination, stereognosis and tactile localization were normal.

The cerebrospinal fluid was under a pressure of 80 mm. water. The fluid contained nine lymphocytes per c.mm. Total protein 0·14 grm. per cent. Lange curve 3332221110. Wassermann reaction negative.

Five weeks after admission a severe chest infection occurred and the patient died; no further change having taken place in the neurological findings. At autopsy only the brain was removed. The internal surface of the skull showed some pressure marking, not of recent origin. There was a marked cerebellar pressure cone, consisting partly of the cerebellar tonsils but chiefly of swollen medulla. The pons felt firmer than normal. Section across the brain-stem showed a rather soft rounded tumour occupying the left half of the tegmental region of the pons in its lower part and projecting forward into the 4th ventricle. At the upper level of the pons it occupied only a small area between the medial lemniscus and the iter of Sylvius. In the medulla it affected almost the whole of the left half. Histologically the tumour was a glioma of the glioma pontis type.

Comment.—This case presented many features which were identical with those of Case 2. It is notable that in this case there was greater quantitative loss of thermal sensibility, and also less marked over-reaction to heat and cold than was found in Case 2. This is in keeping with the suggestion made above that the degree of loss of sensation bears an inverse relation to the degree of over-reaction that may be present over the same area.

Case 4. — T. D., male, aged 49. Admitted to the National Hospital November 27, 1911, under the care of Dr. Howard Tooth.

Complaints.—(1) Weakness and numbness of the left side of the face for three months; (2) weakness of the left arm and leg for three months; (3) headaches and vomiting for three months.

Three months before admission he began to notice that his left arm and leg were weak. At the same time the left side of the face became numb and he developed a left facial paralysis. He also complained of attacks of headache associated with a sense of rotation of objects about him in a clockwise direction. In these attacks he would tend to fall forward or to the left. There had been diplopia with the images vertically above one another. Two months before admission he started to have severe pain in the left side of his face (although that side felt numb). At the same time his left eye became inflamed and rapidly went blind. (This eye was subsequently removed without anæsthesia.) For one month the whole of his right side from the shoulder downwards had felt numb He had always been rather deaf on the left, but deafness had become complete on that side during the present illness.

Past history.—Major and minor epilepsy for thirty years.

Examination.—There was nystagmus on looking to the right and left, and a rotatory nystagmus on looking upwards. There was marked weakness of the muscles of mastication on the left side. The right corneal reflex was impaired. (The left eye had been removed.) There was loss of all forms of sensation over the distribution of the left 5th nerve. Sensation was normal on the right side of the face. There was an almost complete paralysis of the left side of the face. There was complete nerve deafness on the left side. There was deviation of the palate to the right on phonation. The left palate reflex was absent, the right impaired. Power in the limbs was good, but there was gross inco-ordination of cerebellar type in the left arm and leg. The limbs on the left side were hypotonic. The knee and ankle jerks were brisker on the right side than on the left, and the abdominal reflexes were absent. He tended to fall to the left while walking.

Sensation.—(1) *"Spontaneous"*: The right arm and leg were subject to a "dreadful numb sensation." The right side seemed asleep. He complained of pain in the right arm and leg and in the genitalia—pins and needles "like electricity." This did not involve his face. He noticed the sensation on turning over in bed and on putting the right foot to the ground.

(2) *Touch*: Cotton-wool was appreciated on hairless and hair-covered parts on both sides. On the whole of the right side of the body cotton-wool caused an abnormal response—a numb, tingling sensation. Von Frey's hairs were well appreciated on both sides.

(3) *Tickling and scraping*: This produced a subnormal response on the right side.

(4) *Pain*: He failed to appreciate even the most forcible pricking on the right side of the body, but said that it caused "that funny sensation I cannot describe." it seemed to radiate all over the part and on one occasion went up to his neck.

(5) *Thermal sensibility*: There was complete loss of perception of all degrees of heat or cold on the right side of the body, including that part of the right side of the head not in the trigeminal area. There was no over-reaction.

(6) Position sense, stereognosis, two-point discrimination and tactile localization were normal throughout.

This patient eventually came to autopsy. The left side of the pons was found to be enlarged and felt abnormally soft. There was a moderate hydrocephalus. A large tumour was found occupying the left side of the pons varioli. It extended posteriorly to just beyond the caudal margin of the restiform body, and here destroyed the dorsilateral margin of the medulla. Anteriorly it reached the point at which the brachia conjunctiva separate from the cerebellum. Throughout its length its dorsi-medial portion lay free in the 4th ventricle. Histologically, the tumour was an infiltrating glioma which was, however, fairly well limited from the surrounding normal brain tissue. Serial section showed that there was little or no damage to tracts on the right side. On the left the damage was extensive. The medial lemniscus, however, had almost entirely escaped. Gowers' tract was largely degenerated above the tumour.

Comment.—This case is similar in many respects to the two preceding cases. The over-reaction was less marked, however, and the quantitative loss of sensation was much greater. No observation was made as to the presence or absence of delay in the perception of pain.

I wish to thank Dr. Gordon Holmes for his invaluable criticism and advice, and for his permission to publish details of the cases under his care; also Dr. Denis Brinton for permission to publish details of Case 3.

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THE VENOUS DRAINAGE OF THE BRAIN, WITH SPECIAL REFERENCE TO THE GALENIC SYSTEM.

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ON the basis of experiments on dogs, Bedford reported (1937) that a collateral circulation becomes rapidly established after occlusion of the great vein of Galen (*Vena magna cerebri*). He concluded, therefore, that the hydrocephalus which was occasionally found by Dandy and Blackfan (1914) and by Gulecke (1930), in dogs in which the vein had been blocked experimentally, was not directly due to the occlusion of the vein. In a subsequent series of experiments, Bedford (1934) occluded the great vein of Galen in monkeys. These animals likewise failed to show hydrocephalus after a survival period of six weeks, but no evidence was found of the manner in which the collateral circulation had developed in the choroidal plexus and the basal ganglia. Schwartz and Fink (1925-26), who injected the great vein of Galen in human brains, were unable to reach positive conclusions regarding the collaterals of the vein and the venous drainage of the basal ganglia, and they suggested that these investigations required to be further extended. A study of the venous system is also of importance for the question of the localization and pathogenesis of certain infections and other pathological conditions which have been described in the monkey and in Man, and are known to have a definite topographical relationship to the venous channels of the grey and white matter. The present paper comprises a report of an investigation, based on the examination of normal and experimental material, with the object of elucidating these details of the circulation.

TECHNIQUE.

The method employed to investigate the problem of the collateral circulation in the monkey was based on the following considerations:—

(1) The occlusion of one of the small veins of Galen leads to a unilateral hyperæmia; this allows a comparison between the normal vessels and the venous channels which are dilated in order to cope with an increased amount of blood.

(2) Bedford's animals were killed after a comparatively long time, and within this period all kinds of vascular adjustments may have taken place, as is suggested by the rather transitory effect which follows the occlusion of the surface veins in the rhesus monkey. In our experience this operation is followed by a very pronounced hyperæmia, producing small cortical hæmorrhages, which completely disappears within forty-eight hours. It was decided, therefore, to kill the first of the experimental animals immediately after the operation, the second after twenty-four hours, and the third animal after a longer period of time. The last animal, however, died after a few hours and our observations, therefore, are so far based on acute experiments only.

(3) Instead of injecting the venous system of the monkey, it appeared preferable to stain the vessels with Pickworth's stain (1934), a method which consists of the histological application of a blood stain. As a result of the reaction between sodium nitroprusside and the hæmoglobin of the red corpuscles, the latter appear blue-black. This method is in some respects more reliable than injection, for in the latter case the injection-mass may not always enter the small vessels everywhere. In most cases the manner of arborization which has been so clearly described by Pfeifer (1930) materially aids in differentiating arteries and veins, except in the vessels of very small calibre. However, it is a disadvantage of Pickworth's method that the degree of the chemical reaction is variable. It may be quite successful in some sections of one single set but it may be very weak in the others: intensive stains may sometimes last for many weeks, whereas other equally well-stained specimens may fade overnight. On the whole Pickworth's method had distinct advantages, as will become more apparent in the description.[1]

(4) The small vein of Galen was coagulated, as it was impracticable to use a silver-clip in the small field between the lower surface of the corpus callosum and the roof of the third ventricle.

A report of the experiment performed in the third animal will serve to describe the operative procedure.

A bilateral skin-flap with a frontal base was reflected and two large bone-flaps were turned down separately, the left flap in the upper part of the field extending across the midline. The dura was incised at a distance of about 1 cm. from the median plane on either side of the longitudinal sinus, and the incision carried upwards towards the edges of the sinus and well down into the temporal region after a bilateral decompression had been done. After reflecting the four dural flaps, practically the whole convexity of both hemispheres was exposed together with the frontal, precentral, parietal and occipital veins. The right parietal vein was coagulated and divided. The right hemisphere was gently retracted from the falx in this region and the posterior part of the callosal body exposed and split, with practically no bleeding, by means of a blunt dental needle, the tip of the needle emerging between the two crura fornicis. In order to avoid possible damage to the great vein of Galen, division of the callosal fibres did not include the posterior border of the splenium. After widening the opening, a small amount of cerebrospinal fluid escaped from the 3rd ventricle, the roof of which was opened in one small place. The roof was not injured in the other animals. The fluid was sucked away and the laterally-situated fibres of the corpus callosum pulled to the right until the roof of the ventricle and the plexus, forming a small, brownish, longitudinal strip of tissue, could be seen. On further retraction, the right vein of Galen was brought into view. It was slightly elevated with a small pair of forceps and the coagulating current applied. As a result the distal part of the vessel increased to about twice its size and remained enlarged until the beginning of the closure which was begun a few minutes later. There was no hæmorrhage throughout the operation. However, there was some swelling of the brain so that the dura could not be closed. The two bone flaps were sutured in position and the closure of the skin completed. Immediately after death, the brains were fixed in Pickworth's solution for eight hours. They were then cut into frozen sections of 250 μ thickness and stained.

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[1] The nerve cells should not stain. In one of our animals, however, a composite picture was obtained and the vessels and the cell-layers could be clearly seen. No explanation for this reaction could be given and the staining of the cells could not be reproduced in other specimens.

EXAMINATION OF SECTIONS.

A common feature of the sections was a hyperæmia on the operated side which was very marked in the third case and moderate but distinct in the first two animals. The hyperæmia was most obvious in the regions adjacent to the corpus callosum but was hardly evident in the frontal and occipital areas as compared with normal brains and with the corresponding areas of the same brain on the opposite side. There was no hyperæmia in the basal part of the temporal lobe. It is interesting to note that, in the human brains injected through the great vein of Galen, this region of the temporal lobe also showed very little injection. On closer inspection a certain degree of hyperæmia was also found on the unoperated side, which was undoubtedly caused by the œdema following the occlusion of the vein and the resulting increase of intracranial pressure. The hyperæmia was manifested in the following changes:—

(*a*) The veins were enlarged and the number of the macroscopically visible vessels was increased.

(*b*) Some of the veins were tortuous. Although a number of veins in the white matter were found to be somewhat tortuous in the brain of the normal monkey stained by Pickworth's method, as well as in brains of monkeys injected with carmine-gelatine, this tortuosity was less marked than in the operated brains, and is explained by a certain amount of shrinkage that occurs during the fixing of the specimens. The increased tortuosity due to hyperæmia of the veins was accompanied by an enlargement of their calibre and a narrowing of the perivascular space.

(*c*) Where there is a regular distribution of the vessels, as for instance in the head of the caudate nucleus, a pattern of regularly arranged spots with indistinct outlines was observed when the specimens were looked at under a low power. These spots correspond to the cross-sections of congested vessels which are surrounded by smaller rami and post-capillaries given off in a star-shaped manner.

(*d*) There were perivascular hæmorrhages beneath the ependyma covering the caudate nucleus (fig. 1).

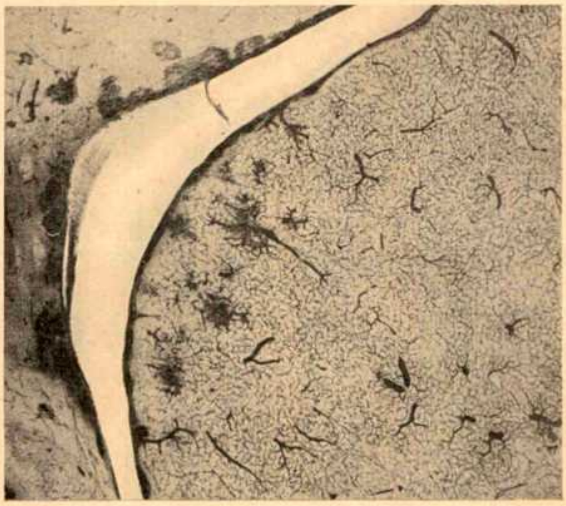

FIG. 1.—Section showing hyperæmic areas in the head of the caudate nucleus and subependymal perivascular hæmorrhages. (× 40.)

(*e*) The capillary loops could be beautifully seen and large numbers of them formed continuous black lines, in contrast to the normal picture of a sodium nitroprusside stain in which the capillary vessels almost exclusively form dotted lines (the stained red corpuscles being separated from each other by short irregular intervals). This is a feature which obviously cannot be brought out by injection of the vascular system.

DISTRIBUTION OF THE VEINS.

The small vein of Galen and its tributaries, the anterior and posterior terminal, the septal and epithalamic veins, were grossly dilated, while the chorioidal vein and the other vessels in the plexus did not differ in any respect from the normal.

The terminal veins.—The tributaries of the terminal veins cross the surface of the head and the tail of the caudate nucleus, forming the *transverse caudate veins* (figs. 2 and 3). They disappear in the region of the lateral angle of the lateral ventricle between the lower surface of the corpus callosum and the upper surface of the caudate nucleus. Here, numerous cross-sections of vessels can be seen which lie close together and represent the continuation of those transverse veins which have changed their direction abruptly to form the *longitudinal caudate veins* (figs. 2 and 3). The latter skirt the superior border of the caudate body, the bulk of the vessels derived from the anterior terminal vein being directed forwards, whereas most of the veins arising from the posterior terminal vein run backwards.

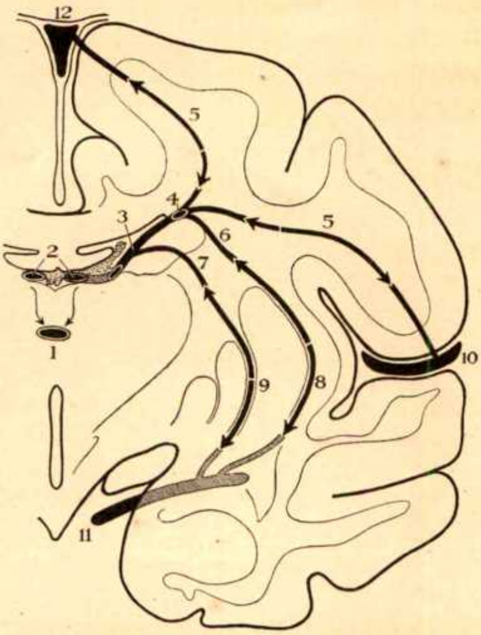

FIG. 2.—Diagrammatic cross-section through the brain of a Rhesus monkey, showing the connexions between the Galenic system and the veins on the surface of the brain: (1) Great vein of Galen; (2) small veins of Galen; (3) transverse caudate vein; (4) longitudinal caudate vein; (5) venous channels, connecting the great vein of Galen with the superior longitudinal sinus and the superficial Sylvian vein; (6) and (7) superior external and internal lenticular veins; (8) and (9) inferior external and internal lenticular veins; (10) superficial sylvian vein; (11) deep sylvian vein; (12) superior sagittal sinus.

This arrangement can be more clearly understood from the injection experiments made on human brains where these vessels were dissected out, as will be described later. The longitudinal veins were grossly enlarged in the third animal, and moderately so in the others. They give rise, from a topographical point of view, to two groups of vessels, the first being situated in the white matter, the second in the basal ganglia (fig. 2).

The first group is represented by three different sub-divisions which, however, share the common feature that their course follows, with a few exceptions, the course of the callosal fibres from the lateral angle of the ventricle to the cortex on the medial surface and the convexity of the cerebral hemisphere.

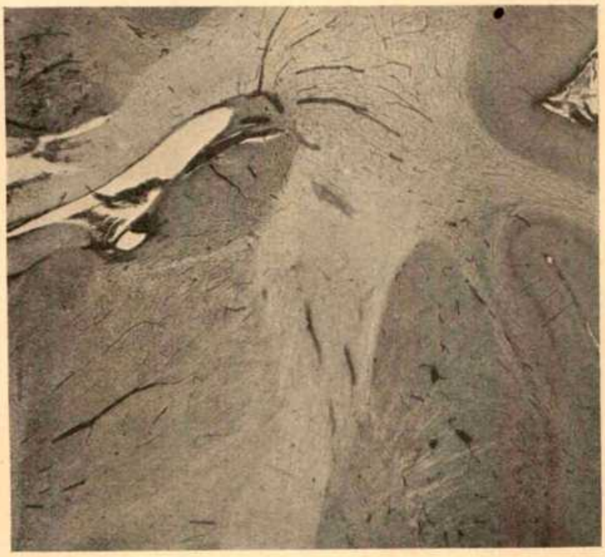

FIG. 3.—Section showing the fan-like arrangement of subventricular veins, and the superior lenticular veins perforating the internal capsule. (× 25.)

The vessels forming the first group are: (i) Coarse capillary networks which begin a very short distance from the lateral ventricular wall and extend throughout the white matter and the cortex as a continuous plexus (fig. 3). They can be most clearly seen in the suprasylvian region.

(ii) Small subventricular veins which arise from the longitudinal veins in a fan-like manner and soon break up into capillary plexuses which are continuous with the network just described. Deep to the cortex the plexuses are drained by subcortical veins which penetrate the cortex, receive a great number of branches from the dense capillary network of the grey cortical matter, and finally enter the veins on the surface of the brain. The plexus of the white matter forms, as a whole, an irregular pattern, but the larger postcapillaries, which connect the capillaries with the venules, join the latter very often at right angles (figs. 4 and 7).

(iii) Large veins (fig. 4), some of which are even macroscopically visible over wide areas in suitable sections and which, in the experiments, were very much enlarged and frequently tortuous. The calibre of these veins

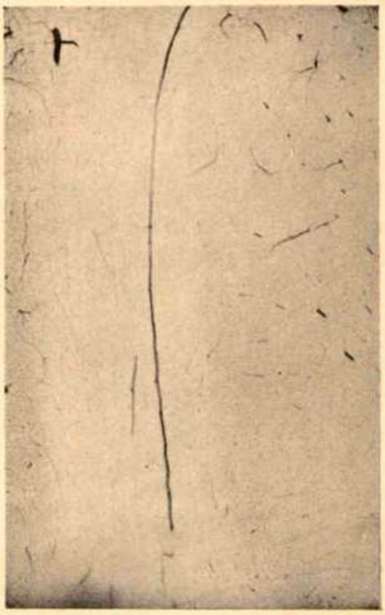

FIG. 4.—Section showing intracerebral anastomotic veins, joined at right angles by smaller veins. (× 25.)

does not appreciably change during their course. Moreover, they do not break up into capillaries but are joined only at relatively long intervals and in most instances at right angles by short venules and sometimes by capillaries without intervening larger vessels. The larger veins are therefore certainly linked up with the capillary plexus, but there is some disproportion between the size of these vessels and their scanty connexions. Exceptions to this rule are infrequent, and veins of larger size and constant calibre with a great number of connexions are only rarely found. Whatever additional functions they may have, these veins must represent anastomoses between the Galenic system and the veins on the brain-surface. They may therefore be called *intracerebral anastomotic veins.*

(iv) Numerous transitional types of venous channel. Sometimes veins arising from the capillary network close to the ventricle soon attain a larger size and travel towards the periphery, thus covering, like an anastomotic vein, a considerable distance (fig. 5). In one instance, an anastomotic vein was found to be formed by two larger veins joining each other at an acute angle. While "pure" types are so frequently encountered that they fully justify the establishment of fairly distinct anatomical and consequently physiological units, the frequent occurrence of all kinds of transitional forms must be emphasized.

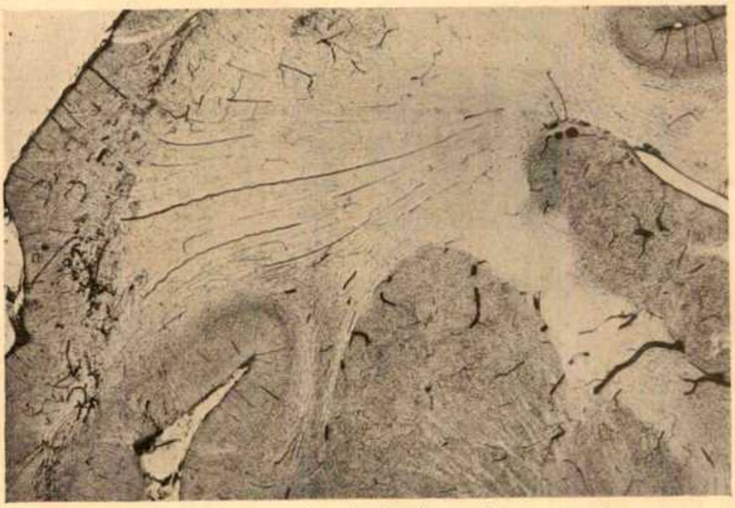

FIG. 5.—Section showing a long subcortical vein, arising near the outer ventricular angle. Longitudinal caudate and superior lenticular veins are also seen. (× 25.)

The second group of veins is formed by branches of the transverse caudate veins, which enter the brain-substance between the thalamus and the caudate nucleus or the grey matter of the caudate body itself. Other rami of this group come off from the longitudinal caudate veins where they participate in the formation of the "fan-pattern." Common features of these vessels are their large size and their relationship to the basal ganglia (figs. 2, 3 and 5).

(i) The veins which rise in the ventricular angle can be seen in the region of the upper border of the caudate nucleus throughout its curvature. They perforate the internal capsule and reach the lateral surface of the putamen or in some cases actually traverse the outer layers of the latter as *superior external lenticular veins*, to break up into a great number of venules which collect the blood from a very dense capillary network. The basal layers of these capillary areas are drained by venules which unite and form the *inferior external lenticular veins.* These large vessels converge towards the anterior perforated space, crossing the anterior surface of the anterior commissure where it leaves the substance of the putamen and enters the external capsule. Finally these vessels open into the deep Sylvian vein.

(ii) The rami of the transverse caudate veins which are given off before the latter reach the outer angle of the lateral ventricle enter the inner layers of the putamen, the medullary lamina of the lenticular body and the globus pallidus. They branch into smaller vessels and finally break up into a capillary network which is continuous with the capillary area just described and the system of the inferior internal lenticular veins which cross the anterior commissure within the substance of the lenticular body and join the deep Sylvian vein more medially. The inferior lenticular veins emerge at the base of the brain where they intermingle with the inferior lenticular arteries entering the anterior perforated space. The more posteriorly placed inferior lenticular veins perforate the roof of the inferior horn of the lateral ventricle and open into the inferior chorioidal veins.

The septal vein.—The description of this vein will be postponed, as the course of the tributaries of this vessel is rather complicated and can be much better seen in the human brain.

The epithalamic vein.—After occlusion of one of the small veins of Galen there was also a certain amount of hyperæmia in the thalamus, particularly apparent in its anterior nucleus, the capillaries of which are very large and densely arranged. The thalamus drains its blood partly into the epithalamic vein and partly through the inferior thalamic veins into the posterior communicating vein which lies underneath the posterior perforated space and connects the two basilar veins.

The veins of the chorioid plexus.—The appearance of these vessels did not differ from that of those in the normal plexus, nor was there any difference between the two sides in the animals operated upon. The blood of the plexus is partly drained by the small vein of Galen through the superior chorioidal vein, as already described by Testut (1929) and by Bedford (1934), and partly by the inferior chorioidal vein which joins the basilar vein. There was no asymmetry of the ventricles due to a hydrocephalus on the operated side.

Injection of Human Brains.

Two human brains were injected with a hot solution of carmine-gelatine under heavy pressure. The cannula was inserted into the commencement of the straight sinus after the inferior longitudinal sinus had been occluded by hæmostatic forceps. Two hemispheres were sliced into coronal sections, one was divided into horizontal sections, and in the fourth hemisphere the ventricular veins and their tributaries were dissected out and followed into the brain-substance as far as possible. The findings were identical in the two injected specimens.

(1) *The intracranial anastomoses of the great vein of Galen.*

Transverse caudate veins, corresponding to those already described in the monkey, were demonstrated (fig. 6). They cross the surface of the caudate nucleus and disappear in the region of the angle of the lateral ventricle where they enter the brain-substance. If the ependyma is carefully incised along the upper border of the caudate nucleus after the corpus callosum had been removed, the course of these vessels can be followed further by piecemeal removal of the white matter. At the region of the ventricular angle the veins, the course of which has already been described above, change their direction. The longitudinal veins divide at acute angles into a number of branches, the resulting rami, therefore, lying close

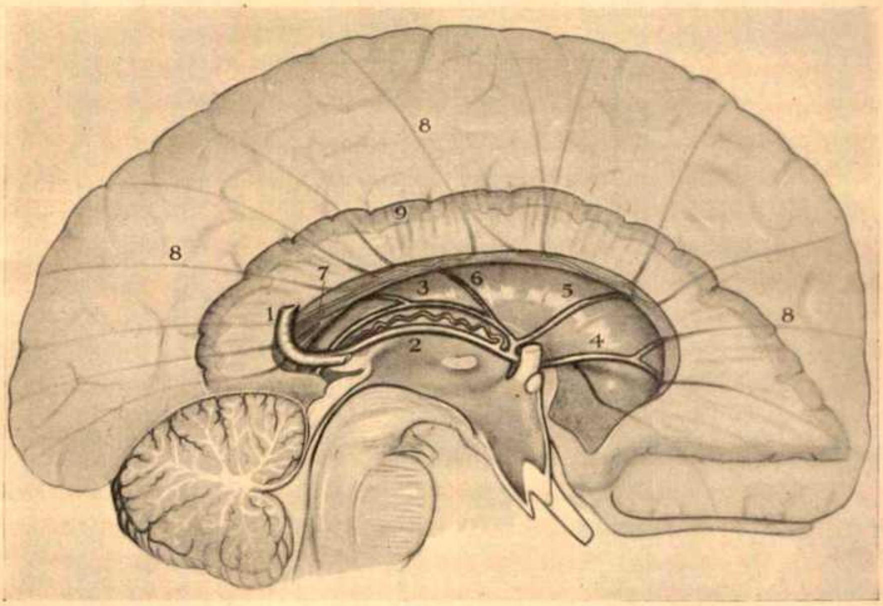

FIG. 6.—Diagram illustrating the distribution of the tributaries of the Galenic system of veins: (1) Great vein of Galen; (2) small vein of Galen; (3) posterior terminal vein; (4) septal vein; (5) anterior terminal vein; (6) transverse caudate vein; (7) longitudinal caudate veins; (8) intracerebral anastomic veins; (9) cut surface of cortex.

together for relatively long distances. As a result of this peculiar arrangement whole groups of vessels are found in cross-sections through this region in the monkey as well as in Man, where they are macroscopically visible. Later on these vessels become directed laterally and upwards, and in the region of the body of the lateral ventricle their numerous rami, too, are also seen to lie in the transverse plane. The rami arising in the wall of the anterior horn are directed forwards, and in the region of the ventricular triangle and the posterior horn backwards. Just as in the monkey, it could be seen that whereas the size of many vessels diminishes rapidly in their course, the larger vessels maintain their size and can be followed into the white matter for about one inch from their point of origin. The further course of these vessels (which undoubtedly correspond to the anastomotic veins seen in the monkey) can be demonstrated much better in horizontal and coronal sections. The veins closely follow the stream of the callosal fibres, this arrangement being particularly striking in the regions of the forceps anterior and forceps posterior where definite " venous radiations " were encountered. The diameter of these vessels is about half a millimetre and no ramifications could be seen in the centrum semiovale in microscopical sections stained with picric acid.

The system of the septal veins deserves a special consideration. It was rather difficult to get a clear idea of the arrangement of the tributaries of the septal vein in the monkey, but a more definite conception applicable to both monkey and Man was finally gained by correlating the histological findings in the monkey with the macroscopical features elicited by slicing and dissecting the human brain. In the injected brains the communicating rami derived from the septal vein and the most anteriorly placed branches of the anterior terminal vein dive down under the base of the head of the caudate nucleus and the putamen where they are caught by rostral fibres of the corpus callosum and carried towards the base of the frontal lobe. The remaining branches of the anterior terminal vein travel chiefly with the callosal fibres above the rostrum to the convexity of the frontal lobe.

A large vein is evident in the anterior part of the internal capsule in the monkey and in Man, an illustration of which is given in Testut's textbook (1929). This vessel connects the system of the superior lenticular veins, where they penetrate the internal capsule, with the veins on the surface of the frontal lobe. It has no relationship to the callosal fibres but is embedded in the anterior peduncle of the thalamus and the region of the fronto-pontine tract.

On cutting the brain in the median plane a great number of veins were encountered in the splenium, while the remaining part of the callosal body showed only a few vessels. The splenial veins are directed downwards and forwards towards the posterior part of the commissure of the fornix. They connect the veins of the fornix with the posterior callosal vein, thus draining the blood from the medial wall of the lateral ventricle into the Galenic system. The question of a possible connexion of the splenial veins with the veins of the plexus of the 3rd ventricle, however, could not be decided.

The gross appearance of the injected veins in the basal ganglia in Man resembles that seen in the monkey. The injection of the caudate and the lenticular nuclei is fairly uniform, whereas, in the thalamus, the injection-mass is confined to its superior half which corresponds to the territory of the epithalamic vein. The hypothalamus, however, shows a more marked injection, derived from the veins at the base of the brain which communicate with the great vein of Galen through the extracerebral anastomoses of this vessel.

(2) *The extracerebral anastomoses of the great vein of Galen.*

The injection-mass was found to have entered the following areas:—

(1) The whole occipital lobe and large parts of the adjacent parietal region through the occipital vein. In one case, almost the whole posterior part of the hemisphere, including the Rolandic vein, was filled with carmine-gelatin.

(2) The medial surface of the brain above the posterior half of the callosal body and the splenium through the posterior callosal vein.

(3) Through the basilar vein, the region of the limen insulæ, and the inferior half of the superficial Sylvian and the whole of the deep Sylvian vein, the veins on the orbital surface of the frontal lobe, the inferior lenticular veins and the veins supplying the pes pedunculi, the substantia nigra, the corpus Luysii, the nucleus ruber, the zona incerta, and probably also the basal part of the thalamus.

(4) Part of the inferior half of the cerebellum and a number of pontine vessels through the superior cerebellar vein.

DISCUSSION.

Lorente de Nò (1928), Luna (1928), Cobb (1931) and Pfeifer (1930) have shown that the capillaries of the cerebral vessels form a large common network, and the last-named was able to demonstrate anastomoses between precapillaries and vessels of even larger size, arteries as well as veins. The results of our investigations may be applied to certain aspects of the cerebral circulation, without going into details which have already been described and discussed by Pfeifer such as, for instance, the so-called pressure-veins, suction-arteries, and so forth.

There is some controversy in the literature about the relationship of the intracerebral vessels to the fibre-systems. Duret (1874) claimed that the vessels closely follow the paths of the fibres, whereas, in the opinion of Pfeifer, the arrangement of the vessels is largely independent of the fibres. The study of our material suggests that, on the whole, the veins are more apt to follow the fibre systems than the arteries, particularly the venules, the medium-sized veins and the vast majority of the anastomotic veins. Exceptions are the most medially placed anastomotic veins in the region of the angle of the lateral ventricle, and the superior lenticular veins, the course of which is almost at a right angle to the fibres of the callosal body and the internal capsule respectively. The arrangement of the postcapillaries, likewise, is largely independent of the fibre-systems.

We cannot agree with Schwartz and Fink, who claim that the territory of the vein of Galen is chiefly represented by the white matter and that this vein drains only comparatively small parts of the basal ganglia, for the large size of the superior lenticular veins, found in our specimens, is against such an assumption.

The general arrangement of the blood-vessels in the white matter suggest that the circulation takes place in the following way. Blood entering the white substance through a cortical artery is distributed to the capillaries from which it enters the nearest vein to return to the brain-surface (fig. 7). Blood reaching the periventricular white matter through the basal arteries is drained by the great vein of Galen. The individual arteries and veins are connected by the common capillary network supplying and draining certain areas within the white matter. The boundaries of these regions must be considered as more or less variable. The regional independence of the arteries is greater than that of the veins, as evidenced by the pathological effects following the occlusion of an artery; on the other hand, the venous territories reveal a very marked degree of overlapping since connecting links trespass across the boundaries of the venous territories at frequent intervals. Between the territories of the basal and cortical arteries no distinct anatomical boundaries exist, but there is a definite physiological boundary: in contrast to this, the territory of the cortical veins extends, in certain regions, far down to the ventricular wall, while the drainage area of a vein opening into a vessel in the neighbourhood of the ventricle may extend far up towards the subcortical layers. In still other regions, the territories of the cortical veins and the ventricular veins may even be identical. The manner in which the large anastomotic

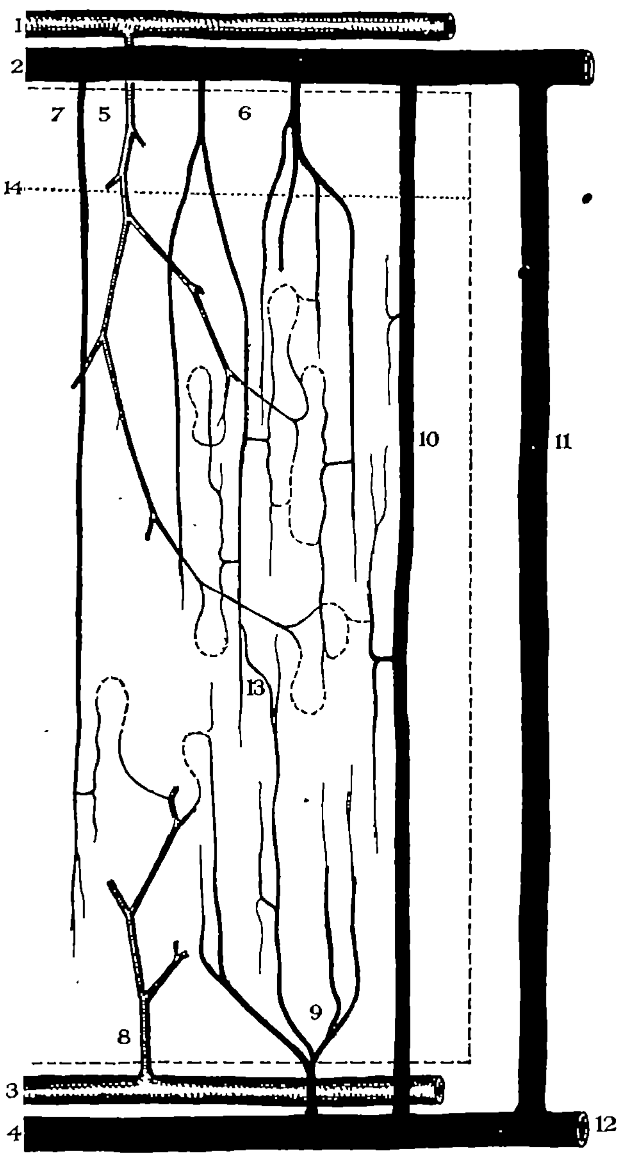

FIG. 7.—Diagram showing the venous circulation in the white matter and the connexions between the superficial cortical and the ventricular veins through the intra- and extracerebral anatomotic veins: (1) Pial artery; (2) pial vein; (3) basal artery; (4) basal vein; (5) cortical artery; (6) cortical-vein; (7) cortical and long subcortical vein; (8) subventricular artery; (9) subventricular vein; (10) intracerebral anatomotic vein; (11) extracerebral anatomotic vein; (12) great vein of Galen; (13) intervenous anastomosis; (14) junction of cortex and white matter.

veins are joined by the small venules suggests that the direction of the blood-flow in the big veins may normally proceed in either direction. Through the connecting vessels the blood is conducted directly, making a short-cut into the cortical and ventricular veins respectively. The network-like arrangement prevailing in the venous system makes it evident that the blood may be shifted from one more or less arbitrarily outlined area into other regions as necessity may arise. The function of the large intracerebral veins would be, as a whole, to facilitiate the drainage of the capillary areas, to cope with a temporary increase in the blood-flow, and to connect the large ventricular with the surface veins. By these anastomotic veins, therefore, pressure-difference between these territories can readily be equalized. The function of the intra- and extra-cerebral anastomotic veins, as for instance the basal vein of Rosenthal, are probably quite similar.

The intracerebral anastomotic veins were seen by Pfeifer (1930) and other investigators (in the human and in the cat's brain). Pfeifer, however, makes only a general statement that a small amount of the venous blood of the white matter is not drained by the surface veins but flows towards the ventricles where there are various possibilities of connexion with the basal veins. Duret (1874) succeeded in injecting the great vein of Galen from one of the cortical veins, and mentions the anastomotic veins as "*veins médullaires*" (Pfeifer's "*Markvenen*"), but he does not describe their topographical arrangement and the manner in which they are linked up with the large tributaries of the great vein of Galen in the region of the lateral ventricle and with the venules and capillaries of the white matter.

The anastomotic veins seem to be completely absent where there are many vessels of varying calibre in a given area, as for instance in the basal ganglia. The same applies to a still greater degree to the plexus choriodeus with its rich system of communicating blood-vessels. This plexus, therefore, shows no evidence at all of hyperæmia if one of its venous outlets is blocked. Bedford, having occluded the great vein of Galen, did not find an enlargement of the ventricular system six weeks after the operation, but mentions that a transitory hyperæmia might have been present a short time after the operation. The anatomical and clinical evidence, however, in our experimental animals in which the ventricle was not opened does not suggest an increased production of cerebrospinal fluid.

The effects following the occlusion of a vein in the grey and the white matter are, as a rule, transitory, and changes affecting circumscribed areas following venous occlusion are infrequent; their occurrence depends on the rate at which the occlusion takes place. No account of untoward results following the occlusion of one small vein of Galen in man could be found in the literature, the vessels and their tributaries being able to adjust themselves to gradually increased local as well as general pressure. In conditions of acute or sudden occlusion, or suddenly increased pressure, however, as in a case of thrombosis in adults (A. Meyer—personal communication), birth-injuries (Schwartz and Fink, 1927), and, in our experiments, hæmorrhages in the soft substance of the caudate nucleus occur. The author has in his collection encephalograms showing the very uncommon feature of a grossly irregular outline of the shadow of the caudate nucleus in an enlarged anterior horn; this can best be explained by the presence here of old scar-tissue, formed as a result of a considerable hæmorrhage having occurred in the subependymal layers of the caudate body at birth.

The importance of the venous system of the brain has been realized for some time, not only in relation to traumatic but also to other pathological conditions. Meyer and Cook (1936) have put forward the view that the peculiar network-like localization of hypermyelinized scars in cases of status marmoratus may be due to peculiarities in the arrangement of the venous blood-vessels. In post-vaccinal encephalitis and in encephalitis following measles the characteristic lesions are situated around the veins of larger calibre (Pette, 1931). The same applies to the demyelinization of the white matter as described in monkeys by Schob (1931). Meyer and Cook believe that in diffuse sclerosis also the veins are related to the localization of the process. Putnam (1937) has called attention to a possible venous origin of disseminated and diffuse sclerosis. Finley (1937) found that the distribution of encephalitis associated with vaccination, variola and measles was dependent primarily on the distribution of the larger veins, and suggested the injection of a contrast-medium into the cerebral vessels, believing that it would be found that certain types of veins are more likely to be involved. While injecting human brains, we made the following observations which may have a bearing upon this and similar questions: when, in brains removed some time after death and in which the brain-substance has undergone some softening, hot carmine-gelatine solution is forced into the great vein of Galen under heavy pressure, extravasations may be produced, chiefly in the region of the angle of the lateral ventricle. These extravasations closely simulate the distribution and even the shape of plaques in advanced cases of multiple sclerosis. Some authors claim that the ventricular fluid plays a part in determining the localization of the disease, but it seems possible that the plaques may only be found in this area of the ventricular wall because they have a definite topographical relationship to the veins which are crowded together in the region of the lateral ventricular angle. Further, the flat plaques which are sometimes situated in the subependymal region above the ventricle can be accounted for by the presence of veins which run parallel to the roof of the lateral ventricle, in association with the callosal fibres.

SUMMARY.

(1) The occlusion of one small vein of Galen after splitting the posterior part of the corpus callosum in a series of monkeys produces a unilateral hyperæmia in certain parts of the brain-stem and of the hemispheres on the operated side, and facilitates the investigation of the vessels draining the blood from this and the neighbouring areas.

(2) The great vein of Galen drains partly the capillary network of the white matter of the cerebral hemispheres in the region of the lateral ventricle, the basal ganglia, and the chorioid plexus of the forebrain, but these structures can also be drained under certain circumstances by veins situated on the surface of the brain.

(3) The Galenic system, therefore, is not an anatomical and much less a functional unit, and forms no exception to the general principle of the plexiform arrangement of the venous system.

(4) In the more extensive areas of white matter, where the capillaries are scanty, large venous channels, referred to as *intracerebral anastomotic veins*, are present. They arise in the region of the angle of the lateral ventricle from the anterior horn backwards as far as the posterior horn, their distribution following the arrangement of the callosal fibres. They establish the main intracerebral connexions between the great vein of Galen and the veins on the surface of the brain.

(5) No anastomotic veins were found in the basal ganglia where their absence may be related to the density and the richness of the capillaries and the larger vessels.

(6) The distribution of the larger veins in the basal ganglia is described, and attention is called to differences in the angio-architecture of the thalamus.

(7) The drainage areas of the great vein of Galen and the large veins of the brain-surface overlap to a very large extent, and widely separated areas, as for instance the pons, the frontal and occipital lobes, can be injected through the surface communication of this vein.

(8) There was no hyperæmia in the chorioid plexus and no hydrocephalus as the result of the occlusion of the vein. There were, however, numerous hæmorrhages in the head of the caudate nucleus, which were

analogous to hæmorrhages observed in various clinical conditions related to a suddenly increased intravenous pressure.

(9) Artificially produced perivenous extravasations of a contrast-medium closely simulate the shape and the distribution of plaques in advanced stages of multiple sclerosis.

I wish to express my thanks to Professor Le Gros Clark at whose instigation this experimental study of the venous drainage of the brain was initiated, and under whose direction it was carried out. I wish also gratefully to acknowledge the assistance of a grant from the Nuffield Committee for the Advancement of Medicine.

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NEUROLOGICAL SEQUELÆ OF "KERNICTERUS".

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KERNICTERUS: DEFINITION AND ÆTIOLOGY.

THE question of the relationship between diseases of the liver and certain brain lesions has not ceased to excite the minds of neurologists since the fundamental description by Kinnier Wilson of "Progressive lenticular degeneration."

That such a relationship exists was suggested as early as 1875 by Orth who, in his investigation of severe neonatal jaundice, described a condition of the brain in which a yellow discoloration was localized to certain nuclei in the brain, brain-stem and cerebellum. The question of jaundice of the brain in children dying from severe neonatal jaundice was more extensively examined by Schmorl (1904) who gave pathological descriptions of two types of jaundice of the central nervous system.

In the first of these, the systemic jaundice was associated with a diffuse golden colour of the whole brain substance. On section of the brain in this condition, small pinpoint areas of degeneration, known as Virchow's fatty granular areas, were noted in the white matter. These areas, which were the size of a lentil and of a golden white colour macroscopically, were found on microscopical examination to consist largely of fatty granular cells. Under the microscope, the whole brain was found indiscriminately charged with a fine golden colour, while bilirubin crystals were present in the blood-vessels and cerebrospinal fluid. This type of jaundice of the brain, with which we are not here concerned, has been very seldom described in the literature since. In fact Moebius found it as occurring in only three cases out of 300 which had died from severe jaundice of the newly-born.

The second type described by Schmorl, for which he coined the term "Kernicterus," was of the same nature as that noted by Orth. In it the yellow pigmentation is confined to very circumscribed areas. Of the 120 cases examined by Schmorl this condition was found in six. The yellow pigment was localized in his cases to the basal ganglia and medulla. Briefly, it may be said that though confined to the nuclear masses of the brain it was not present in them all. In every case the lenticular nucleus was involved with a tendency to spare the caudate nucleus and the thalamus. The subthalamic nuclei were particularly affected. Other structures which frequently showed this yellow discoloration were the cornu Ammonis, the dentate nuclei and the inferior olives. Some staining of the cranial nerve nuclei in the medulla and the dorsal grey matter of the upper spinal cord also occurred.

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Microscopically the ganglion cells in the areas pigmented looked glassy and homogeneous with a tendency towards cytolysis. The axis cylinders in these areas were also stained.

Since 1904 cases of Kernicterus, a number of which have been confirmed on post-mortem examination, have been reported by Beneke (1907), Pfannensteil (1908), Esch (1908), Pfaltzer (1914), Hart (1917), Ylppö (1918), Palm (1915), Thorling (1921), Hawksley and Lightwood (1934), and Zimmerman and Yannet (1933). The last-named authors, in reporting with considerable pathological detail two cases of Kernicterus, made an analysis of the literature on this subject then available.

Briefly, their findings led them to conclude that Kernicterus, far from being a disease *sui generis,* is associated exclusively with icterus gravis neonatorum, and that overt septic or obstructive jaundice play little part in its ætiology. They also reported that it was confined to severe jaundice of the newborn and that a case in adult life had not been confirmed. They enumerate the structures most frequently affected in order of severity as the subthalamic nuclei, the basal ganglia, the cornu Ammonis, the inferior olives, the dentate nuclei, the thalami and some of the nuclei of the cranial nerves in the medulla. In severe cases the grey matter of the upper cervical cord is affected also. They report that there was always degeneration of the ganglion cells in the areas pigmented and in fact that the intensity of the jaundice as noted with the naked eye ran parallel to the degenerative changes noted microscopically.

There is little in this view that, in the light of recent knowledge, we can cavil at, though the sole association of Kernicterus with icterus gravis neonatorum is not acceptable. Recent additions to the literature by Biemond and van Creveld (1937) has made it clear that septic jaundice may be a cause, while Pasachoff (1935) has reported a case of congenital atresia of the bile ducts with erythroblastosis and Kernicterus.

On the clinical side several siblings are frequently affected, the parturition being normal and the child being born healthy but developing severe icterus within the first few days. Symptoms referable to involvement of the central nervous system manifest themselves within the next twenty-four hours. The commonest of such symptoms are tonic and clonic movements going on to convulsions in some cases.

Between these attacks there is usually a generalized hypertonia of the muscles with a tendency towards opisthotonos. Drowsiness and apathy with spells of hypotonia have been reported but not as invariable features. Children surviving the immediate illness develop choreo-athetoid movements and emotional instability at or about the fourth week. Zimmerman and Yannet consider that sufficient evidence is not yet available on which a clinical diagnosis could be made but suggest that the following three criteria should be fulfilled before even a tentative diagnosis is permissible.

(1) The child is normal at birth.

(2) Jaundice develops before the second day.

(3) Signs of involvement of the central nervous system are present. Hawksley and Lightwood (1934) consider this attitude a conservative and reasonable one. Fatal termination attends most cases by the fifth day after the onset of the jaundice.

In discussing the pathogenesis of Kernicterus the two primary problems, the ætiology of the jaundice and that of the localization in the centres affected, must be considered separately.

The question of the jaundice does not concern us here and it may be briefly pointed out that theories are as numerous as facts are scanty. In discussing icterus gravis neonatoıum it has been held at one time or another that it is due to: (1) A primary dysfunction of the blood; (2) liver intoxication either maternal or fœtal: (3) a fœtal septicæmia; (4) maternal intoxication.

The consenus of opinion is in favour of the first of these suggestions, considerable evidence having in recent years been brought forward in its favour. It must be emphasized, however, that many writers on this subject think that the erythroblastosis which is commonly found in it may be secondary to hæmolysis of a toxic origin. It has been shown that Kernicterus may be associated with jaundice from a number of causes, e.g. obstruction of the bile passages (Pasachoff (1935, Ylppö (1918)) and hepatitis (Biemond and van Creveld (1937)) as well as hæmolysis, so that this question is not now so important as was thought at one time.

The second question, namely, the localization of the pigmentation in certain areas, is of more immediate interest. Orth held the view that the jaundice in the brain masses was secondary to death of the cells from some other cause. He believed that this occurred much as an intra-vital dye is taken up more easily by dead or dying cells than by living ones. The cause of the death of the cells in these areas has been variously attributed to: (1) A peculiar attraction of certain ganglion cells for the bile pigment, resulting in their death; (2) the pigmentation of the ganglion cells subsequent to their destruction by the bile salts (Orth); (3) the destruction of the ganglion cells by ischæmia or birth trauma and their later pigmentation; (4) A congenital inferiority (maldevelopment) of brain acting as a predisposing factor in the localization of bile salts in the areas affected.

EXPERIMENTAL STUDIES.

The question of localized brain lesions in association with liver disease has been examined from the experimental point of view. In this field, the most important work has been done by Mella (1924), Pollak (1921), Fuchs (1914), and Crandall and Weil (1933).

The work of Fuchs, using guanidine as a liver poison (also with an Ecks fistula), has made it clear that damage to the liver by itself is capable of producing nervous disease. Pollak, who examined these brains, noted true inflammation and dropping out of ganglion cells but was unable to show distinctive or circumscribed change. However, Mella, using intraperitoneal injections of manganese, was able to produce in *Macacus rhesus* changes localized to the putamen and caudate nuclei. Here the neurons were shrunken and pyknotic, many having completely lost their nuclei. Scattered areas of mild gliosis with demyelination were also seen. Though the injections had been given intraperitoneally it is of interest to note that, in two of the animals, fibrosis and hæmorrhage had occurred in the livers and that these were the only organs, apart from the brain, in which any change could be seen.

Crandall and Weil, using ligature of the common bile duct and an Ecks fistula as their method of choice, were able to cause in the rat a constant involvement of the corpus striatum. In one of their cases it was seen that the cornu Ammonis and the fascia dentata were similarly involved. Though the findings in experiments on dogs were not so constant nor localized, yet the mass of this experimental evidence goes into the balance in emphasizing the close connection which exists between lesions of the liver and of the brain and especially of the basal ganglia.

In an effort to find a basis for the localization of the lesions so constantly noted C. and O. Vogt (1920) pointed to the difference in architectonic structure in various areas and postulated a "physico-chemical pathoclisis" as the differentiating agent. Spielmeyer (1930), not entirely satisfied with this vague hypothesis, investigated the blood supply of different brain structures. From this he reported that the corpus striatum and cornu Ammonis have a relatively poor blood supply and this indicated that they might be expected to suffer first in diseases affecting the blood supply to the brain.

Further work by A. Meyer (1936) has shown that the regions which have normally a rich iron deposit, e.g. the globus pallidus and the zona rubra of the substantia nigra, or calcium deposit, e.g. the anterior globus pallidus, inferior olives, dentate nuclei and cornu Ammonis, are the regions most commonly injured in anæmia of the brain whether it be from carbon monoxide, carbon dioxide or morphine poisoning. Further, he has shown that in rodents, in which the globus pallidus contains no iron deposit, this area is not susceptible to anæmia.

Recently some evidence has been brought in favour of the view that a predisposing factor in the condition may be maldevelopment of the brain. It is known that when such a retardation has occurred the balance between the blood and the cerebrospinal fluid is upset. Biemond and van Creveld noted a lack of normal development in one of their cases, while Brouwer (1936), quoting three cases of Ten Rea's, suggested that the same ætiological factor played an important part. It has been a constant difficulty that though many children may die of severe jaundice only a small percentage show Kernicterus. In the light of the information available to-day, the hypothesis which best fits the facts seems to be one which includes a degree of mal-development as the primary factor responsible, while localization in the structure involved depends on a relative ischæmia of these areas.

SEQUELÆ OF KERNICTERUS.

The pathological description of all cases of Kernicterus up to 1935 was confined to children who had died during the acute illness and in whom the nuclei already noted were still stained yellow. Though it was felt that a number of children must have survived the neonatal attack, no pathological account of such cases was attempted until the above date when Zimmerman and Yannet described a case which had survived with signs of cerebral damage. Including this American case, only five cases have been reported which the post-mortem examination has proved to show sequelæ of Kernicterus. Of these, four have been reported from Holland, two by Biemond and van Creveld and one each by Cornelia de Lange and by van Westrieren and de Lange (1937).

PERSONAL INVESTIGATIONS.

The two cases on which we have carried out our pathological examination show the sequelæ of Kernicterus while we consider that the third case also belongs to this group. The infants were severely jaundiced in the neonatal period and later showed symptoms referable to involvement of the central nervous system.

Case I.—We are indebted to Dr. B. Kounine for the clinical history of the earlier stages of the disease and for the opportunity of making a post-mortem examination in this case.

There is no consanguinity of parents. The first child, male, now 7 years old, is mentally bright and well developed. This child, who was normal at birth, developed on the fifth day jaundice which persisted for three months. For the first six weeks he did not gain weight, while an unusually large and protruding abdomen was a conspicuous feature until the second year.

The second child, a female (D. P.), was delivered on July 14, 1938, in a normal and easy manner. For the first few days she took the breast, but on the third day became jaundiced and refused to breast feed. After this she was given glucose and barley water. By the fourth day the jaundice had increased considerably and had intensified in colour. On the night of the fifth day the temperature rose to 105° F., the head became retracted, and convulsions, accompanied by screaming and vomiting, set in. In these convulsive attacks the child assumed a position of opisthotonos with the legs adducted, the knees partially flexed, and the feet inverted. On the following day the arms became involved with abduction and internal rotation at the shoulder joint; they were flexed to a right angle at the elbow, the wrists were flexed and the fists clenched. On the afternoon of the sixth day, the diagnosis of familial jaundice was made and an injection of 10 c.c. of the father's whole blood was given. On the following day the baby, when seen by another doctor, looked so ill that he advised against further treatment as he did not think the child could survive the brain injury. The father, however, insisted and another injection of 15 c.c. of whole blood was given, after which the temperature fell to 102° F. and the retraction of the head and spasm of the neck diminished. Two more injections of 5 c.c. of the father's blood were given, after which the child improved remarkably. The temperature became normal, the jaundice disappeared and the spasticity greatly diminished by about a week after the first injection. Maximum improvement was noted by about the tenth day after the commencement of the treatment, though there was still considerable spasm of the neck and the fists remained clenched. A neurologist who saw the baby about this time did not discover any gross abnormality and gave a good prognosis. Physically, after this date, the child continued to develop normally, taking her feeds well and putting on weight. At the beginning of the eighth week, in addition to the retrocolic spasm which had persisted and the clenched fists, peculiar movements of the eyes in which the eyeballs rolled up and down began to occur. Though the child at this date seemed to take no notice of her surroundings she could follow a light when her head was supported. An ophthalmologist made the diagnosis of optic atrophy and blindness. The Wassermann reaction was negative.

She was admitted to the National Hospital under Dr. Macdonald Critchley on

September 9, 1938. On examination, the child lay on her right side with her head thrown back and turned a little to the right. The skull was abnormal in shape, the occiput being prominent and jutting over the retrocolic muscles, which were in a state of spasm. The head, for this reason, could not be easily flexed. Some vision was present and the eye movements were full and normal. There was no squint, except in brief bouts, in which the eyes were rotated downward and inward, producing crossed strabismus. The other cranial nerves appeared normal. The upper limbs were still spastic, with the hands half clenched. No involuntary movements were seen, but the voluntary ones were clumsily carried out and lacking in vigour. The child resented interference and cried easily.

Sensation was apparently normal. One day, while in hospital, the child had a series of tonic fits relieved by chloral. In these fits, the right side of the face was drawn up, the right arm and leg being extended. A position of opisthotonos was assumed, and the eyes rolled downwards and converged. A scream heralded the onset. At four and a half months the child died of an intercurrent infection at the Central Middlesex Hospital, where by the kindness of the Superintendent a post-mortem examination was carried out by Dr. J. G. Greenfield.

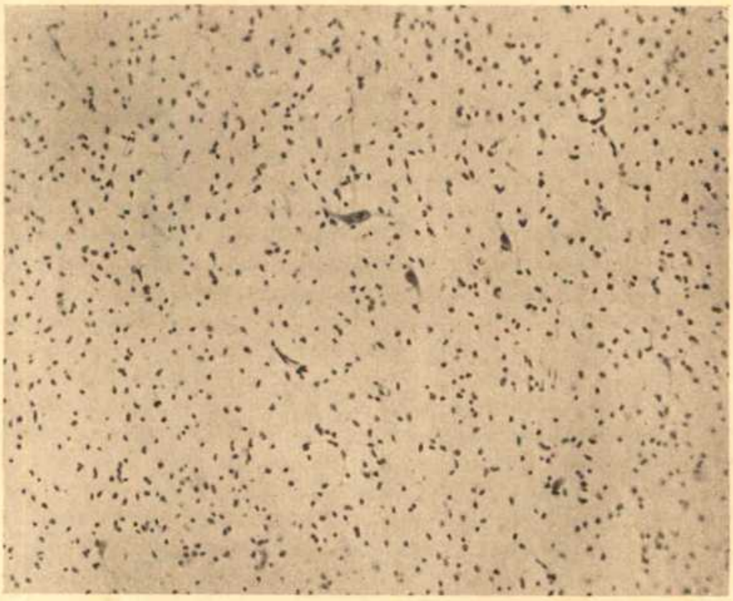
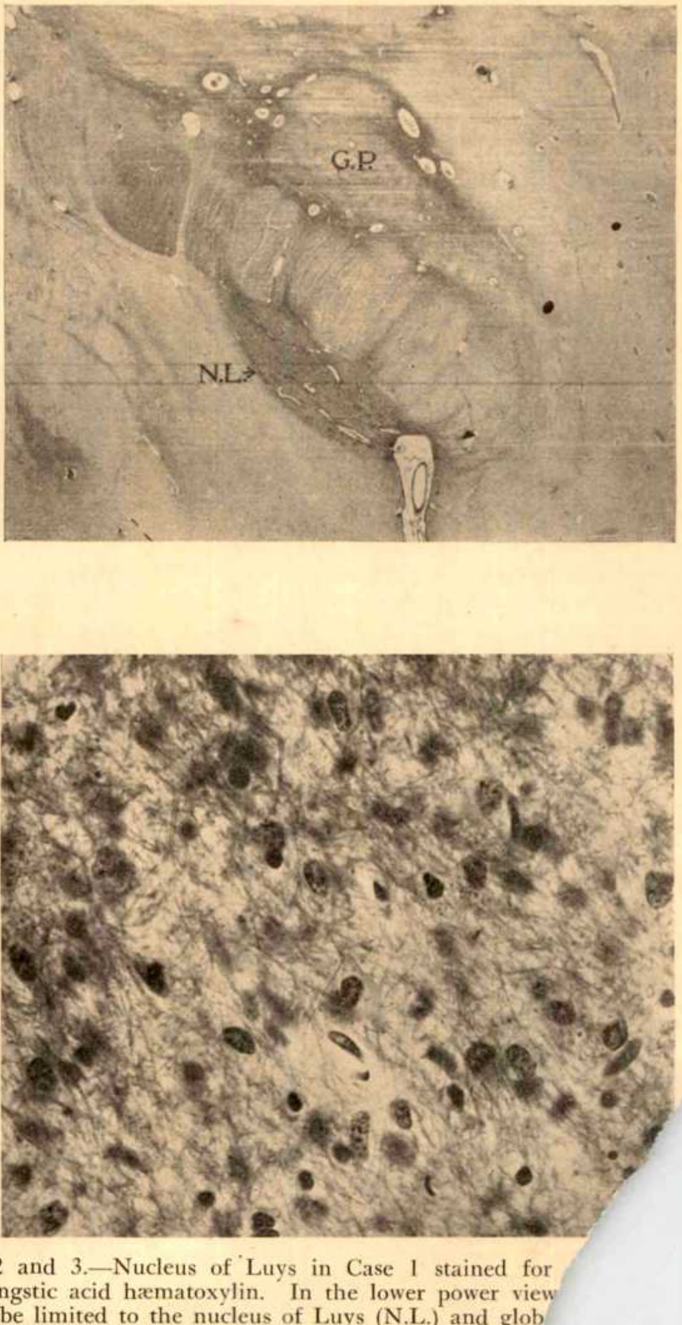


FIG. 1 (*Case* 1).—Section of the globus pallidus stained by Nissl's method, and showing great poverty of ganglion cells. Those that remain are shrunken.

Pathological examination.—The brain and cord appeared normal. On section the globus pallidus looked unduly white and shrunken. The spleen and liver were normal.

The following methods were used in the histological examination; Gros-Bielschowsky, Nissl, Loyez, Mallory's phosphotungstic acid hæmatoxylin and iron hæmatoxylin with van Gieson on paraffin and celloidin sections, and scharlach R. on frozen sections.



FIGS. 2 and 3.—Nucleus of Luys in Case 1 stained for
phosphotungstic acid hæmatoxylin. In the lower power view
is seen to be limited to the nucleus of Luys (N.L.) and glob
to the lines of the fibres connecting these across the internal
astrocytic cells and fibres can be seen. No nerve cells
illustrated.

The globus pallidus on both sides was sclerosed. Its ganglion cells had almost completely disappeared, only sparse shrunken cells remaining and those chiefly at the poles (fig. 1). There was throughout this body a great excess of astrocytic nuclei with a fairly dense feltwork of neuroglial fibres. In the putamen, no definite abnormality could be made out ; there was possibly a slight diminution of large cells. No neuroglial fibres could be seen except around the larger vessels. With the Gros-Bielschowsky and Loyez methods there was a considerable diminution in fibres in the central part of the globus pallidus though nowhere had they disappeared completely. In low power views, with myelin stains, this nucleus was obviously shrunken and pale.

In the nucleus subthalamicus bilaterally no ganglion cells could be seen in the central three-quarters but a few were present in the inner and outer poles. The normal structure of the nucleus was replaced by fibrous astrocytes which had caused a dense sclerosis (figs. 2 and 3). In spite of the disappearance of ganglion cells a considerable number of myelin fibres were seen. Some of these fibres were beaded or had terminal knobs.

All parts of the cornu Ammonis and fasciæ dentatæ were shrunken and sclerosed and in the Nissl picture the position of the various structures could only be delimited by the condensation of neuroglial cells and isolated neurons. A few neurons could be seen in the more anterior parts of the subiculum and also a few in the outermost part of the fascia dentata at this level (fig. 8). Throughout the cornu Ammonis and the fasciæ dentatæ there was dense feltwork of neuroglial fibres (fig. 9). Elsewhere in the cerebral cortex the only abnormality seen was that the neurons had a neuroblastic appearance with very small cell bodies. In the cerebellum there was still a well-marked outer granular layer. The internal granular layer and the Purkinje cells were normal.

The red nuclei, the substantia nigra bilaterally, the inferior olives, the dentate nuclei of the cerebellum and the grey matter of brain stem were normal. In the spinal cord the neurons had a normal appearance. In Weigert-Pal preparations the pyramidal tracts showed the pallor normal at this age.

Case 2.—The brain of this case was sent to the laboratory of the National Hospital by the kindness of Dr. Branford Morgan from the Jenny Lind Hospital at Norwich. It was from a female child aged one year. This was the third child
a family of three, the second child of which had died "sometime after birth
an enlarged spleen." The child, who was normal at birth, developed jaundice
e third day and became within the next few days so profoundly affected
doctor in attendance thought there was congenital atresia of the bile ducts.
the jaundice gradually disappeared. By the eighth week the child appeared
and poorly nourished. Shortly after the onset of the jaundice the child
mptoms suggestive of involvement of the basal ganglia. Later rigidity
bs with adductor spasm of the legs became a prominent feature of

on section, the basal ganglia and particularly the globus pallidus
and white. Similar histological stains were used as on the
s child. Microscopically, a greater number of ganglion cells
bus pallidus than in the previous case but those present were
tendency noted in the previous case towards preservation of
also present. There was an excess of astrocytes without an

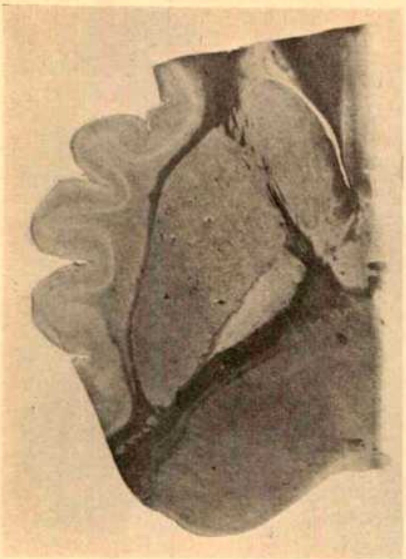


FIG. 4 (*Case* 2).—Section stained for myelin to show the relative pallor and shrinkage of the globus pallidus which normally stains more darkly than the putamen.

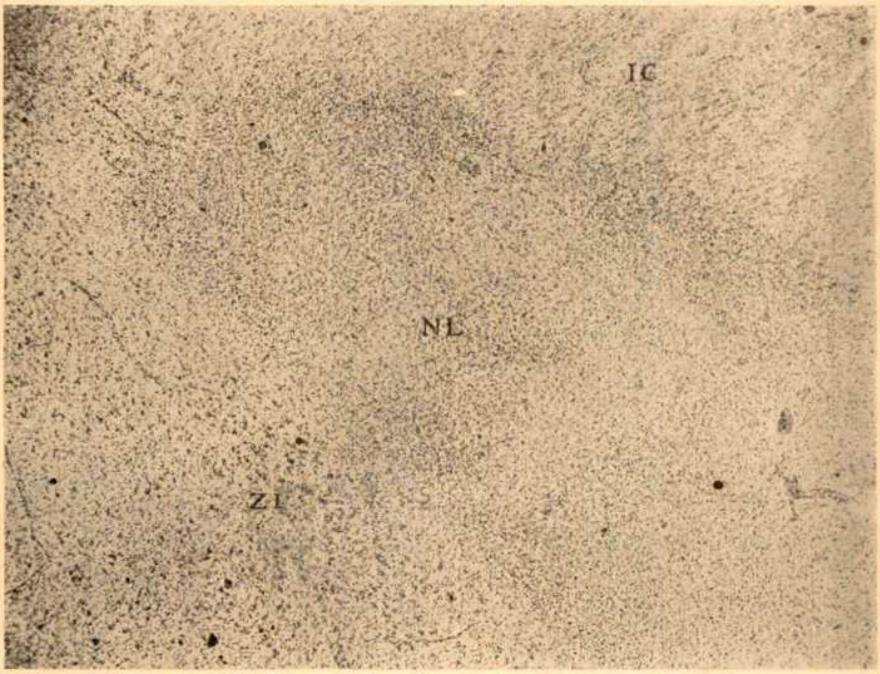


FIG. 5 (*Case* 2).—Nissl's method. The nucleus of Luys (N.L.) consists of small neuroglial nuclei except in its postero-lateral aspect where it is encroached on by the large nerve cells of the zona incerta (Z.I.).

overgrowth of neuroglial fibres. In sections stained for myelin the globus pallidus looked generally paler than the putamen but, when examined under higher microscopic power, a considerable number of myelin fibres were seen to course through it (fig. 4).

The nucleus subthalamicus was remarkably shrunken and had undergone dense neuroglial sclerosis. It was almost entirely devoid of ganglion cells and in its lateral aspect seemed to be encroached upon by the zona incerta which was normally rich in ganglion cells (fig. 5). Most of the ganglion cells of the cerebral cortex had a rather small ragged cell body in which it was found impossible to stain Nissl bodies; an appearance which suggested post-mortem change occurring in nerve cells which had not yet attained their full differentiation.

In sections through the anterior end of the cornu Ammonis and fascia dentata (Band of Giacomini) on both sides the latter was seen to be represented by an irregular band of neurons, in some places only one to two cells thick. The pyramidal cells of the cornu Ammonis appeared to be somewhat rarified at this level. Rather further back the fascia dentata was represented by short bands of cells isolated from one another (fig. 7); for the rest the majority of the cells had disappeared though isolated cells remained. The pyramidal layer of the cornu Ammonis at this level was indicated by isolated neurons and a condensation of astrocytic nuclei. In passing further backwards only the latter could be seen. At all levels there was a slight increase of neuroglial nuclei, without definite sclerosis internal to the fascia dentata.

The substantia nigra bilaterally, the red nuclei, the inferior olives, the dentate nuclei of the cerebellum and the grey matter of the brain stem were normal.

Case 3.—F. B., male, aged 9 years, was admitted to the National Hospital on June 19, 1939, under the care of Dr. Purdon Martin to whom we are indebted for permission to record the case. He is the third child of three normal pregnancies. His elder brother is aged 18 and healthy, while his sister died at 7 years of "acute heart failure."

F. B. was born at full time as a normal vertex presentation. For two days after birth he took his feeds of glucose and water well but on the morning of third day his skin appeared faintly yellow and deepened to a marigold colour by that evening. He now refused food and the doctor who was called in regarded the child as beyond hope. No treatment was prescribed. The motions at this time were foul and of a fatty colour, while the urine was wine coloured and stained the napkins.

This severe jaundice, with the putty coloured stools and dark urine, lasted for a year. At 9 months of age, when brought to the Hospital for Sick Children, he could be described as iris coloured.

The child made no effort to walk or talk until 3 years of age and, during this period, it was found impossible to sit him up in bed as his back was inclined to "give way" suddenly. While nursing him on her arm, the mother noted that his head appeared too heavy for his body and necessitated separate support.

From the end of the first year, until the fifth year, he was troubled with periodical vomiting. At this age it gradually ceased. The vomited material consisted of a green, frothy fluid, while the child appeared perfectly well both before and after the attacks.

Between the fourth and fifth year, the mother noticed certain involuntary movements. While nursing him he would suddenly straighten out his back with such violence that he almost "jumped out of her arms." The upper limbs commenced

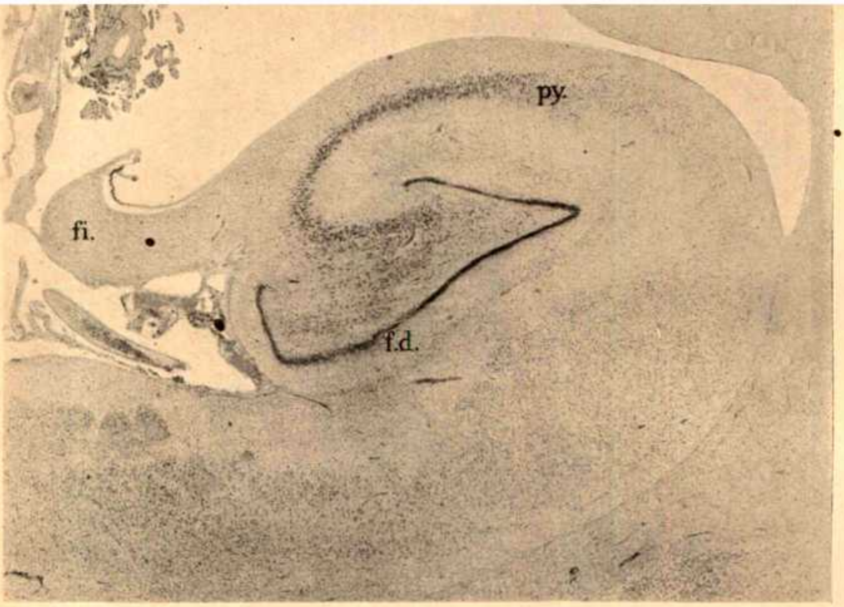


FIG. 6.—Section of normal cornu Ammonis and fimbria, stained by Nissl's method. The level of section corresponds to that in figs. 7, 8 and 9.

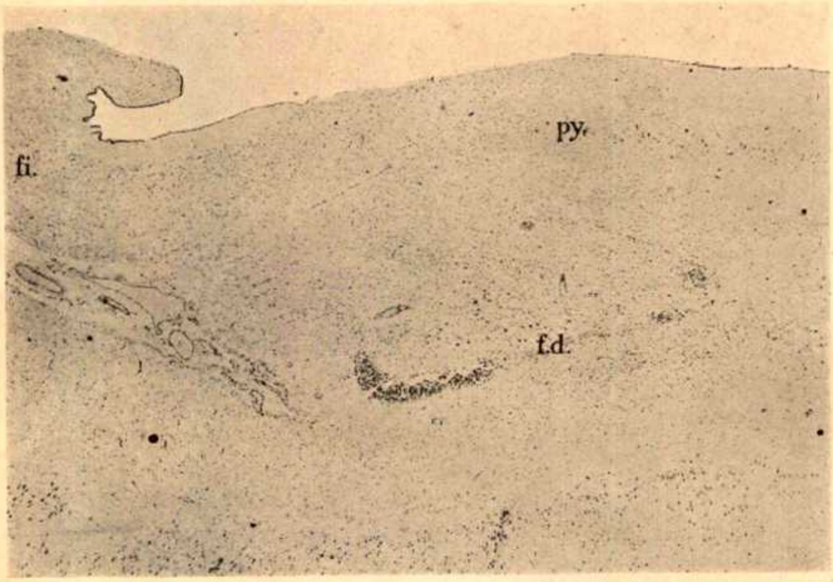
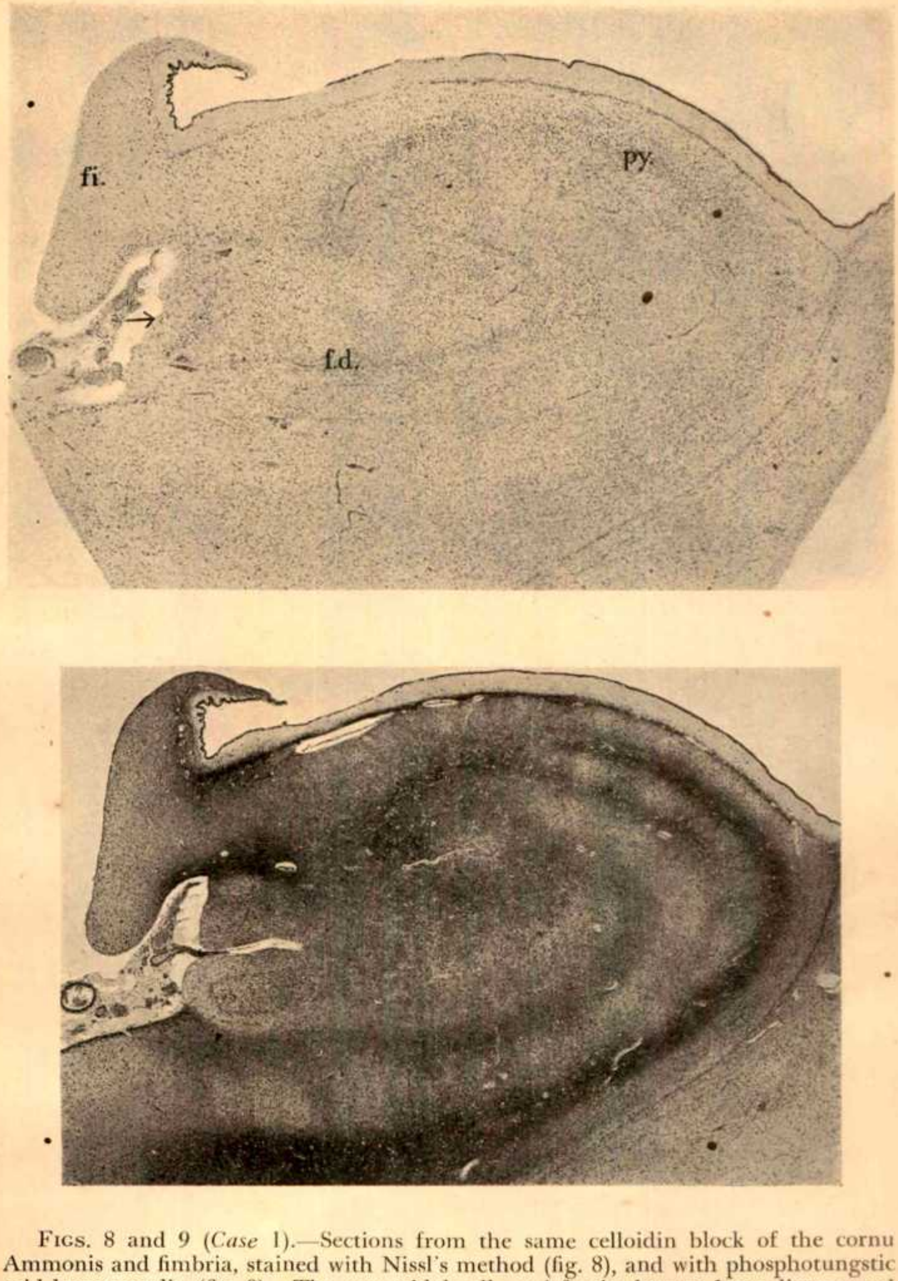


FIG. 7 (*Case* 2).—Section of cornu Ammonis, stained by Nissl's method. A few cells of the fascia dentata are preserved. The rest of the fascia dentata and the pyramidal cells have almost completely disappeared, and astrocytic nuclei have taken their place.

To illustrate article by G. M. Fitz Gerald, J. G. Greenfield and B. Kounine.

PLATE VIII.



FIGS. 8 and 9 (*Case* 1).—Sections from the same celloidin block of the cornu Ammonis and fimbria, stained with Nissl's method (fig. 8), and with phosphotungstic acid hæmatoxylin (fig. 9). The pyramidal cells and fascia dentata have disappeared completely except for a few cells of the fascia dentata at the point indicated by the arrow in fig. 8. There is dense neuroglial sclerosis throughout the cornu Ammonis, especially in the lines of the fibres.

To illustrate article by G. M. Fitz Gerald, J. G. Greenfield and B. Kounine.

to wave about in an irregular manner. She believes that his lower limbs were stiffer then than they are at present.

The family history of the father and the mother was essentially negative.

Examination.—The child, when at rest, appears a normal, well developed boy of 9 years. This resting posture is never long maintained, being disturbed by constant irregular movements, most marked in the face, neck and upper limbs; the lower limbs are least affected. While at rest, his face and particularly his eyes bear out the mother's opinion that he is mentally sound. It has been claimed that he can speak but, except for very occasional words, this is not true when with strangers. As his chief mode of expression he relies on pantomime, at which he is adept. His sense of humour is boyish and acute and there is little evidence of any emotional instability. He is clean in his habits, with full control of his sphincters which he gained at the age of 9 months.

Movements of the face and neck and upper limbs.—For purposes of description these movements have been separated into their component parts but, in life, they are mixed in an altogether irregular manner.

(1) The lips purse together and are sucked in, and this is followed by an effort to chew either the lower or upper lip.

(2) A strong effort to swallow, which includes an extensive out-thrust of the neck and a closure of the eyes.

(3) Retraction of the lips in a toothy smile, followed by a rhythmic chewing movement of the jaws, with a tendency towards sialorrhea.

(4) A flexion and extension movement of the neck often performed with considerable violence.

The upper limbs.—The elbows are extended, forearms pronated, wrists flexed, 1st phalangeal joints flexed or extended with the 2nd and 3rd phalangeal joints flexed. There are large callosities on the dorsal aspect of both hands, evidently caused by pressure when the child is attempting to move around in a sitting posture.

The spontaneous, irregular movements, apart from the general restlessness of the limbs, appear limited to the hands.

The chief movements here are full extension of fingers at the 1st phalangeal joint followed by extension and abduction of 2nd and 3rd joints. Finally, these fingers become adducted and fully flexed at the 2nd and 3rd joints. The full range of movements takes from three to five seconds. These movements are irregular, and though suggestive of athetoid movements, are not classically of this type.

The lower limbs.—The lower limbs, while in bed, appear to be more constantly at rest than the upper limbs or face. They lie extended at the hips and knees, with marked extensor spasm of the feet. The movements which occur are irregular flexion of the legs and knees, with some fanning of the toes. Once or twice in an hour, a more violent clonic spasm supervenes, with the heels beating in rhythm on the bed.

Thus a general description will include grimacing movements of the face, irregular "snake charming" movements of the hands, associated with restlessness of the upper limbs and extensor movements of the lower limbs. Occasional violent movements, in which the child is thrown in a position of opisthotonos, add to the general complexity of the picture.

Walking.—The child can make no effort to walk unassisted and when held up under the arms he dances with uncontrolled irregularity and violence, with arms and legs thrown about regardless of what may be in the way. The picture is suggestive of a tight rope walker losing his balance.

Owing to the involuntary movements and some lack of co-operation, the physical findings were limited.

Physical examination.—The cranial nerves are all normal. Sensation to pin-prick is everywhere appreciated. No localized weakness can be made out. A certain degree of hypotonia of the neck is evident. The upper and lower limbs are rather hypertonic but the degree of this is difficult to estimate.

Reflexes: The tendon reflexes are everywhere brisk, the plantars doubtfully extensor.

The abdomen is normal. There is no increase or decrease in liver or splenic dullness.

LITERATURE REFERRING TO SEQUELÆ OF KERNICTERUS.

Attention must be drawn to two cases described in the German literature before Zimmerman and Yannet's original report of this condition in 1935, by Hoffman and Hausmann (1936) and Burghard and Schleussing (1933). The former of these reports concerns a child who had survived for three and a half months after severe neonatal jaundice. The onset of the jaundice was not until four days after birth. The clinical picture shortly after the onset of the jaundice consisted of " fits," with loss of consciousness, clonus of the facial musculature, spasm of the extremities and opisthotonos. When examined at two months a general increase of the tone of the muscles with exaggerated tendon jerks was the most prominent feature. Pathologically, there was no staining of the basal ganglia or other grey matter, while microscopically the pons, thalamus, globus pallidus and striatum showed perivascular round-celled infiltration. In the case of Burghard and Schleussing the child died at three months. Clinically, the jaundice commenced within the first twenty-four hours. Retroflexion of the head with yellow discoloration of the cerebrospinal fluid was noted by the fifth day. The jaundice commenced to clear up by the eighth day with some improvement in the general features. The child remained subject to attacks of unconsciousness alternating with periods of emotional instability until he died. Another feature of the case was the clenched hands and the mask-like facies. An encephalogram, taken shortly before the infant died, gave evidence of hydrocephalus interus.

Post mortem, the brain was found to be of a general grey golden colour ; though the yellow pigment was scattered diffusely it was particularly obvious in the globus pallidus, subthalamic nucleus and cornu Ammonis bilaterally.

In the white matter, small millet seed softenings were seen which, microscopically, were identical with Virchow's fatty granular areas.

These cases have been quoted frequently in the literature since 1935 as belonging to the chronic Kernicterus group, but it must be doubted if this is a correct view to take of them. In Hoffman and Hausmann's case the jaundice did not develop until four days after birth, certainly an atypical finding. Apart from this, it has repeatedly been emphasized that it is extremely difficult to diagnose such cases ante mortem while the pathological findings of "perivascular round-celled infiltration," a picture never since described in the condition, should be enough finally to decide against its inclusion in this group. Zimmerman and Yannet included Burghard and Schleussing's case in their account as an intermediate type between the acute and chronic Kernicterus. That this view is correct must also be queried. We feel that, with a clinical picture which includes staining of the cerebrospinal fluid and hydrocephalus internus in association with a pathological one including diffuse yellow pigmentation and Virchow's fatty granular areas, it belongs rather to group I of Schmorl in which he noted generalized yellow discoloration and similar small areas of degeneration.

In the analysis of the five previous cases of sequelæ of Kernicterus on which post-mortem examinations have been recorded too great importance cannot be paid to the fact that the pathological findings depended on the severity of the initial attack and also on the length of time the child survived. Thus there is no real anomaly in the various clinical and pathological accounts, which differ in detail though they are basically similar.

These five previous cases have been reported from America and Holland, the Dutch ones by Biemond and van Creveld, C. de Lange and Anna van Westrieren and C. de Lange.

Clinically, these children presented a varied symptomatology, though in all cases some evidence of involvement of the extrapyramidal system, such as choreo-athetoid movements and rigidity, were manifest. Invariably also a marked degree of mental retardation, in many cases approaching the idiot class, was present. Actual blindness or a severe defect in vision has been frequently reported.

Anomalous features confusing this clear cut issue have been noted in a number of these reports. Biemond and van Creveld stated that the rigidity in one of their cases was of the clasp-knife type more suggestive of involvement of the pyramidal tracts than of a deficiency in the extrapyramidal system. C. de Lange noted that movements seemed to lessen the rigidity and that when the child was held up under the arms adductor spasm with actual crossing of the legs could be seen. A finding which she noted also was that the child suffered from periods of excessive motility alternating with periods of somnolence. In two of the five cases emotional instability, such as bouts of crying, without an apparent cause, was recorded.

The pathological picture also varies to some extent, but again certain features are common to all reports.

Macroscopically, it was seen on section of the brain that the structures which are stained yellow in Kernicterus were shrunken and pale.

Histologically, marked loss of ganglion cells and demyelination in the lenticular nucleus has been reported as an invariable finding. C. de Lange and Biemond and van Creveld localize the maximum involvement to the globus pallidus. On the other hand, Zimmerman and Yannet and Anna van Westrieren and C. de Lange indicate that, in their cases, the putamen showed the greater lesion. Such differences are only in degree: all authors agree that both the globus pallidus and putamen show some loss of ganglion cells and demyelination. A more prominent and universal feature was the marked dropping out of cells and demyelination in the subthalamic nuclei. Almost all the descriptions note also a slight increase in the glial fibres in the affected areas. Only two of the five authors report on the condition of the cornu Ammonis and fascia dentata but both report a loss of ganglion cells. A van Westrieren and C. de Lange noted that the anterior nucleus of the thalamus, and especially the centro-median nucleus of Flechsig, showed a change corresponding in type to the one already described as typical for the basal ganglia. The American authors, in addition to their other findings, noted patchy degeneration of the optic nerves and pallor of myelin staining in the lateral columns of the cord. In their case also, the lateral nucleus of the thalamus, and the mamillary infundibular nucleus of the hypothalamus bilaterally, were deficient in ganglion cells. There was a paucity of ganglion cells in the red nuclei and they were unable to identify the substantia nigra. These additional pathological features have not since been reported in the condition.

The sequence of findings relating these cases to acute Kernicterus is complete. A history of severe jaundice shortly after birth was given in all accounts and in many cases several siblings were affected. The onset of the jaundice was rapidly followed by such nervous symptoms as tonic and clonic movements, muscular rigidity and opisthotonos alternating with periods in which the muscles are quite flaccid. Later, if the child survived, and usually within the first four weeks, choreo-athetoid movements appeared. As the child grew older, emotional instability, mental retardation and inability to hold the head up became evident.

Pathologically, the evidence is still more conclusive. The same regions bear the brunt of the affection in both conditions. The chief regions pigmented in Kernicterus are the basal ganglia, subthalamic nuclei, cornu Ammonis and fascia dentata and to a lesser extent the inferior olives and the dentate nuclei of the cerebellum. In the more affected of these regions loss of ganglion cells and demyelination has been consistently reported in the cases which we believe to belong to the group of sequelæ of Kernicterus.

In considering the question why the involvement of the brain is less in the chronic than in the acute cases it must be borne in mind that severe icterus of the newborn is a disease with a high mortality and that it is reasonable to expect that only the least affected children should survive. It must also be considered that though most of the pigmented ganglion cells are dead we cannot be sure that some may be less injured and can regenerate when the noxious influence is removed.

Though in this account we are not attempting to correlate the clinical with the pathological findings, it is interesting to note that, although maximal destruction of the subthalamic nuclei has been an invariable feature of the cases examined, nothing approaching the syndrome of the corpus Luysii has been observed in them. This may be due to the accompanying involvement of basal ganglia.

RELATION OF KERNICTERUS TO OTHER FORMS OF NERVOUS DISEASE.

Any possible relationship between Kernicterus and its sequelæ and other diseases of the nervous system is of interest.

Wilson in his original paper on "Progressive Lenticular Degeneration" suggested that a relationship might well exist between Kernicterus and the condition which he described. In favour of this he cited the fact that there was a circumscribed lesion in both conditions ; in both, the liver appeared to play an important part, and that, among his twelve cases of lenticular degeneration, jaundice was a feature in two and clinical evidence of liver disease was noted in one.

Brouwer (1936), in reviewing the association of diseases of the spleen, liver and brain, discounts such a connection as that suggested by Wilson on the grounds that no lesion in any way related to the cirrhosis of the liver found in hepatolenticular degeneration had been reported as occurring in Kernicterus. This basis for rejecting the suggestion is no longer tenable since cases of Kernicterus began to appear in which some degree of cirrhosis was noted. Biemond and van Creveld found it in one of the livers they examined, while Hawksley and Lightwood found it in seven of their cases. It was formerly thought also that the brain lesions in hepato-lenticular degeneration were very selective, confining themselves to the corpus striatum. That this is not entirely true has been shown by Greenfield, Poynton and Walshe (1926), and others who have noted more diffuse lesions in the brain. This evidence helps to bring Wilson's disease more directly into line with Kernicterus.

Meyer and Earl (1936), in their study of lesions in the basal ganglia in defectives, suggest that a closer study of Kernicterus may yield some evidence concerning the ætiology of *Status dysmyeliniatus* (Hallervorden-Spatz Disease). In this disease the most striking features are a symmetrical and selective demyelination and glial sclerosis with loss of ganglion cells in the globus pallidus, substantia nigra and subthalamic nuclei. A well-marked yellowish brown pigment is found in the glial cells of the globus pallidus. The dentate nuclei, inferior olives and the white matter of the cerebrum and cerebellum were less affected. Between this complete picture found only in the most advanced cases and a pure degeneration of the globus pallidus and zona rubra of the substantia nigra all variations and grades have been described. The structures affected in this disease connect it with Kernicterus though no jaundice or lesion of the liver has yet been reported in it.

Paterson and Carmichael (1924) described a form of familial cerebral degeneration chiefly affecting the lenticular nuclei. Nora Schuster (1925) confirmed this with a similar case. Clinically, the condition is characterized by anorexia, amentia, amaurosis and muscular weakness which develop after three months of normal life. The original paper laid emphasis on severe changes in the cortical cell layer, combined with foci of degeneration and disappearance of nervous elements in the lenticular and caudate nuclei, and in the genu of the internal capsule. Schuster, in confirming these latter changes, did not find any marked difference in the cortical cell layers from the normal. In the original publication it is pointed out that, in the family from which the two cases were obtained, all the children which lived over a few days became jaundiced. This jaundice was never severe and was not recorded in the history of Schuster's child. The distinctions between this condition and the sequelæ of Kernicterus, both on the clinical and pathological side, is obvious. It may, however, bear some relation to Schmorl's first type of cerebral degeneration associated with neonatal jaundice.

An idiopathic and degenerative type of dystonia musculorum deformans is known to affect children. Among others Davison and Goodhart believe that this is not a disease *sui generis* but rather a symptom complex depending on a varied pathological picture. They note that, in their cases, the structure most severely affected was the striatum. These changes consisted of shrinkage, status mormoratus in three cases and status fibrosis in another.

In the clinical description dystonia musculorum deformans is not unlike the sequelæ of Kernicterus and, as it is agreed that it rests on no standard pathological findings, it becomes important to inquire into a possible history of severe neonatal jaundice in such cases.

A number of these suggested relationships may be premature but become of interest when it is remembered that probably 25 per cent. of children suffering from gravis icterus neonatorum survive and that since the introduction of the modern treatment of the condition this percentage, far from declining, must be on the increase. It is also possible that lesser degrees of neonatal jaundice give rise to lesser degrees of brain damage. In an analysis of the cerebral sequelæ of severe jaundice of the newborn undertaken in America by Klingman and Carlson (1937) 675 cases of defectives were examined, in 45 of which a history of jaundice was given. These cases were clinically heterogenous.

A similar investigation, though by no means so extensive, was carried out by Colver (1938) at the Great Ormond Street Hospital for Sick Children. Of nine cases which had survived from a total of fifty with neonatal jaundice, one became mentally deficient, one a mild hemiplegic and one died of bronchopneumonia. That is, on this limited number, over 20 per cent. showed residual nervous symptoms. With these facts in mind, the possibility of nervous sequelæ of Kernicterus being more numerous than perusal of the literature might lead one to imagine, cannot be lightly dismissed.

CONCLUSIONS.

Many cases of disease of the extra-pyramidal system occurring in children appear to have little relation to Kernicterus. Nevertheless, when these symptoms develop during, or shortly after, an attack of severe jaundice the diagnosis becomes probable. In every case in which the clinical diagnosis has been confirmed on post-mortem examination the jaundice has appeared within the first three days in a child who appeared normal at birth.

In the pathological examination of these cases degeneration has been limited to the nuclei most deeply affected in Kernicterus, i.e. subthalamic nuclei, lenticular nuclei and the cornu Ammonis.

SUMMARY.

(1) The literature of Kernicterus and its sequelæ is reviewed.

(2) Three additional cases of sequelæ are reported, two with pathological examinations of the nervous system.

(3) An account of the clinical and pathological evidence on which a diagnosis of the condition may be made has been summarized.

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FALSE DIVERTICULUM OF A LATERAL VENTRICLE CAUSING HEMIPLEGIA IN CHRONIC INTERNAL HYDROCEPHALUS.

BY D. W. C. NORTHFIELD AND DOROTHY S. RUSSELL *

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RUPTURE of the ependyma at some point of the ventricular system, permitting the escape of cerebrospinal fluid into the surrounding tissues, may occur in chronic internal hydrocephalus. If such a rupture allows the fluid to reach the leptomeningeal spaces or to escape by the nose, pressure may be relieved with a consequent remission of symptoms (Meyer, 1905; C. de Lange, 1929; Globus and Silbert, Case 2, 1931). Alternatively the rupture may result in the formation of a false diverticulum of variable size which constitutes an outer sac in the centrum semiovale. In this paper we describe two such cases where the diverticulum caused destruction of the pyramidal tract and hemiplegia.

Case 1.—Left hemiplegia. False diverticulum of right lateral ventricle. Chronic internal hydrocephalus. Chronic traumatic leptomeningitis. Birth injury.

C. P., a boy aged 5 years and 9 months, was kindly referred by Mr. Whitchurch Howell on account of enlargement of the head and a left hemiparesis. He was born in 1929 as a vertex presentation at full term, and, although the second child, labour was prolonged and difficult. The second stage lasted two days, delivery being instrumental under a general anæsthetic. The child's eyes were blackened and they did not open for six weeks, and the head looked misshapen. At the age of 6 months he was taken to the Out-Patients' Department of the Queen's Hospital for Children on account of the size of the head, which measured 46·6 cm. in circumference (normal average 42 cm.). From 1930-1935 the child was under the care of Dr. Harris at St. Bartholomew's Hospital, and we are indebted to him for the clinical records during that period. Development was slower than usual, for the boy did not walk until the age of 2½ years, nor talk until 3½ years old, speech being slow but distinct. His head steadily increased in size with abnormal rapidity. Shortly after he was 3 years old he fell, causing a swelling of the right side of the head; there was no loss of consciousness and the swelling subsided. Later in that year it was noticed that he always held a book to the right of the middle line. When he was nearly 5 years old walking gradually became difficult owing to ataxia and spasticity of the limbs, but the plantar responses at that time were still flexor. About five months before admission to hospital his mother noticed that he dragged his left leg, that the left arm was getting weak, and that the right arm trembled. During the last year or so his head had occasionally ached, but this was not a prominent symptom.

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He was admitted to the Queen's Hospital for Children on October 14, 1935, when the following physical signs were present. The head was very large, its circumference measuring 60·5 cm. (normal average 51 cm.) and the right side appeared to bulge a little; the fontanelles were closed; Macewen's "cracked pot sound" was elicited. The boy carried his head laterally flexed and rotated to the right. Low-grade papillœdema with some secondary atrophy was present; tests of vision were not accurate, but the acuity seemed fair and no hemianopia could be detected. The left pupil reacted well to direct light, but the right poorly; the convergence reflex could not be obtained. There was a right divergent concomitant strabismus. Coarse lateral nystagmus was evoked when he looked to the right; there was complete absence of conjugate deviation of the eyes to the left. A severe left spastic hemiparesis was present, with exaggeration of the tendon reflexes on that side; all abdominal reflexes were diminished; ankle clonus and an extensor plantar response were present on each side, but more marked on the left. Sensory tests were not very dependable; pin-prick, however, was resented less over the left side than over the right side of the body and limbs. He could not walk but he could sit up in bed and feed himself, and he had full control of the sphincters. He was a little backward mentally, but talked intelligently. General physical development was good; he was not obese; there was no polyuria and the urine was normal There were no signs of disease in other systems.

Radiograms of the skull demonstrated the changes characteristic of chronic hydrocephalus, without giving any clue as to the cause. The angle between the floor of the anterior fossa and that of the posterior fossa was flattened, suggesting an early stage of "basilar impression."

The pressure of the cerebrospinal fluid in the ventricles was zero, and the fluid contained 1 cell per c.mm. and 20 mg. per cent. of total protein. The Wassermann reaction of the mother's blood was negative.

It was felt that simple obstructive hydrocephalus due to stenosis of the aqueduct of Sylvius or to lepto-meningeal adhesions as a result of the birth trauma would not account for the hemiparesis, and a diagnosis of tumour was made. A right frontal astrocytoma, or tumour of the brain-stem or of the cranio-buccal pouch, were considered as possibilities.

Dye injected into one lateral ventricle was rapidly recovered from the other, but did not reach the lumbar theca at the end of an hour. Ventriculography demonstrated grossly dilated lateral and third ventricles, without deviation of the septum lucidum or of the third ventricle from the middle line (fig. 1). The posterior part of the right lateral ventricle and the right occipital horn were markedly displaced upwards and outwards (fig. 2). In the lateral view a narrow shadow which crossed the posterior part of the right lateral ventricle obliquely was not explained. The appearances were attributed to a tumour in the right occipital lobe, possibly arising from the tentorium.

On November 12, 1935, an exploratory right parieto-occipital craniotomy was

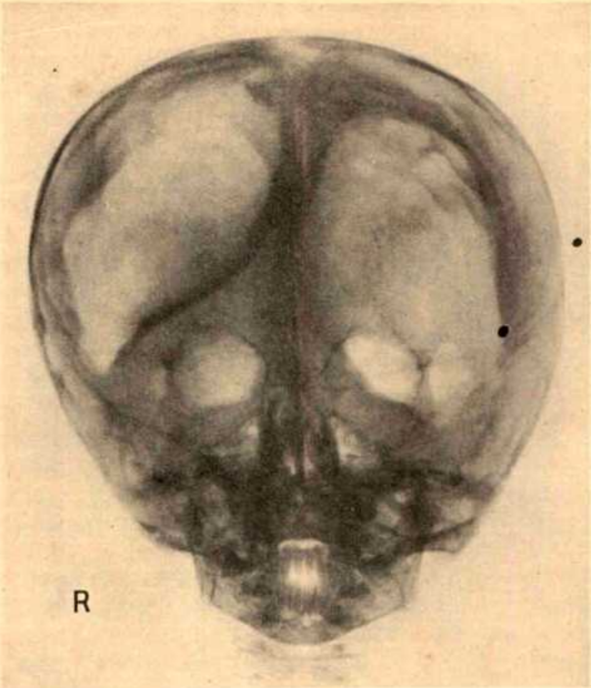


FIG. 1.—*Case 1*.—Ventriculogram in occiput-up position.

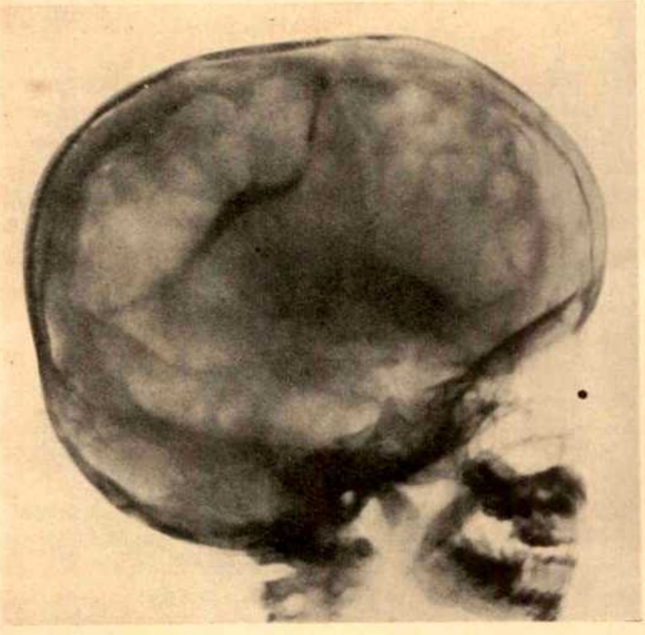


FIG. 2.—*Case 1*. Lateral ventriculogram: right side uppermost.

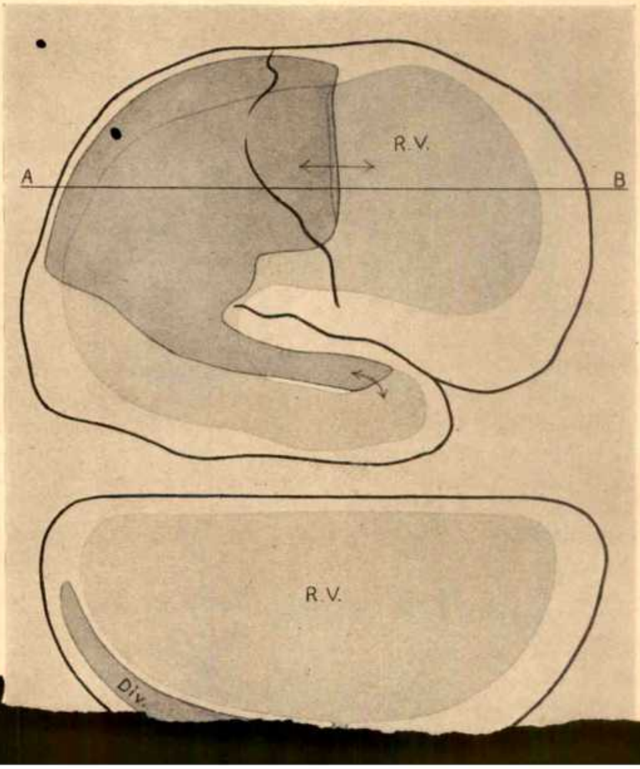
performed. In order to approach the suspected tumour through the dilated ventricle, an oval piece of thin cortex about 4 cm. in diameter was excised from the parietal region. This effected an opening into a cavity which was mistaken for the ventricle, but was, in fact, a diverticulum of the ventricle. One could identify what appeared to be the surprisingly narrow body of the ventricle, and a wide prolongation—its temporal horn. Exploration with a needle did not reveal any tumour, and copious amounts of fluid were obtained when the needle passed medially or caudally ; this fluid must have come from the subjacent ventricle. The tentorium was free from tumour. The child survived the operation but died about a month later from unrelieved hydrocephalus. The operative and ventriculographic findings remained conflicting, and the child was considered to have a brain-stem tumour.

Our thanks are due to Dr. O'Flynn for the report of the cerebrospinal fluid and for the pathological material now to be described.

Examination of brain (P.M. 534. 1934 Appendix).—The brain, hardened in formaldehyde, was symmetrically enlarged, being 51·5 cm. in circumference. The leptomeninges over the cerebral convexities were transparent and moderately engorged, the underlying convolutions broad and flat. There was slight greyish thickening and conspicuous orange-brown pigmentation of the leptomeninges over the basal cisterns, the inferior surface of the cerebellum and the proximal ends of the Sylvian fissures. The cisterna magna and foramen of Majendie were obliterated by tough, matted grey tissue which extended as a less dense layer over the dorsal aspect of the mid-brain to the pineal body. The fourth ventricle was greatly dilated and there was orange pigmentation of the ependyma in the left lateral recess and hinder end of the ventricle. The Sylvian aqueduct was considerably dilated, measuring 0·6 by 0·5 cm. in transverse section at the level of the anterior corpora quadrigemina. The third ventricle was greatly dilated and its ependyma studded with pinhead granulations. The foramina of Monro were symmetrically enlarged, measuring 1·7 cm. in diameter. The septum pellucidum was reduced to a narrow fringe of tissue beneath the fornix. Both lateral ventricles were greatly dilated and their choroid plexuses atrophied. On the right side a diverticulum with smooth, glistening, opaque white walls formed an outer compartment over the dorsal and lateral aspects of the ventricle (figs. 3 and 4). It extended posteriorly to a point just beyond the tip of the occipital horn, ventrally to overlie the temporal horn and anteriorly beneath the Rolandic fissure to end in a vertical slit (3 by 0·9 cm.) communicating with the cavity of the ventricle. The extent and relations of the diverticulum are illustrated in fig. 5. As shown in this diagram a second communication (1·4 by 3·0 cm.) between the ventricle and diverticulum was present over the tip of the temporal horn.

Coronal sections of the brain showed that the combined volume of the ventricle and diverticulum on the right was approximately equal to the volume of the left lateral ventricle (fig. 4). The septum dividing the diverticulum from the ventricle was from 0·1 to 0·4 cm. thick and was everywhere composed of moderately firm, rather congested white matter.

Microscopic examination.—The leptomeninges over the brain-stem and posterior surface of the cerebellum were moderately thickened by fibrosis. They were infiltrated sparsely with polymorphonuclear leucocytes and small lymphocytes, and more densely with large mononuclear cells containing abundant granules of iron pigment. Similar pigment was present in conspicuous amounts in the cytoplasm of astrocytes forming the marginal glia over the brain-stem, upper cervical cord and in the superficial layers of the cerebellar cortex at the summits of the folia. There was an increase in the glia in these areas, especially in those of the cerebellar cortex, and here it was accompanied by destruction of the Purkinje cells and, in many foci, of the granule cells also.



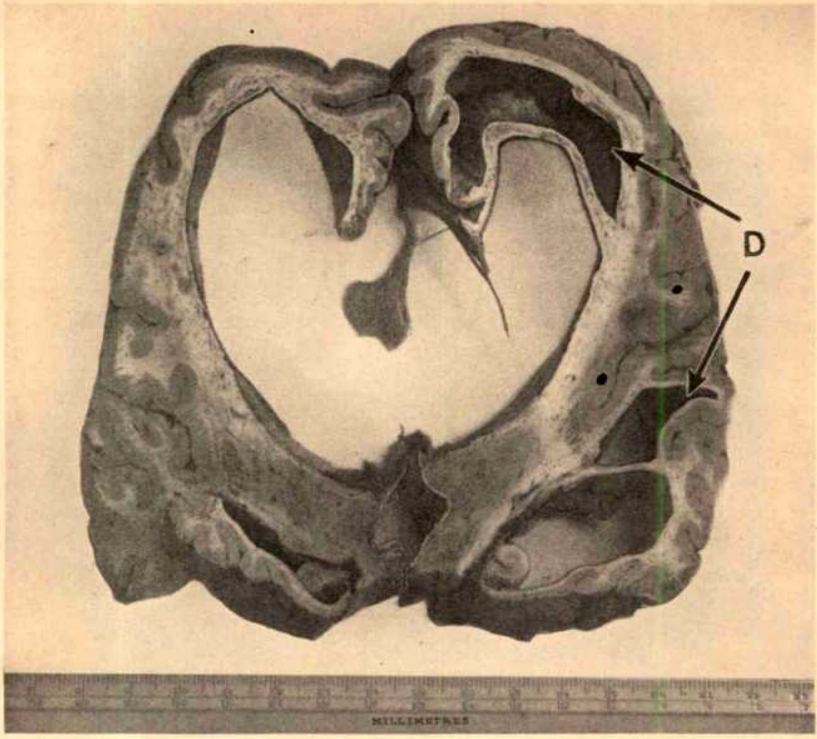


FIG. 3.—*Case 1.* Coronal section of brain through basal ganglia.

demarcation between it and the adjacent white matter was not sharp. The lining of the diverticulum was occasionally coated with a thin layer of collagen fibres, such an area being observed, for example, near the more dorsal orifice of the diverticulum.

Sections through the mid-brain, medulla oblongata and the first cervical segment stained with Loyez' hæmatoxylin show advanced degeneration of the right pyramidal tract.

Case 2.—Left hemiplegia. False diverticulum of right lateral ventricle. Chronic internal hydrocephalus. Acute and chronic leptomeningitis.

E. I., a girl aged 2½ years, was admitted to the London Hospital on December 6, 1934, under the care of Dr. Maitland Jones—to whom we are grateful for the clinical records—on account of enlargement of the head and left spastic hemiplegia. The child was born at full term and the delivery was normal. The head was noticed to be a little large. The baby thrived on the breast, and was weaned at 10 months.

At the age of 9 months the child was feverish and screamed for two weeks. There was no vomiting and no pyrexia, and the appetite was said to be normal. She completely recovered from this disturbance, although her head steadily increased in size more rapidly than normal. Just after her first birthday she was able to walk. At the age of 2 years and 3 months there was an illness similar to the previous one, lasting two weeks, called "meningitis," and characterized by persistent screaming. From that time the mother noticed a more rapid increase in the size of the head, and stiffness and progressive loss of use of the left arm and leg. The child was fretful and slept poorly. Nine weeks before admission the mother suddenly realized that the child had become blind.

When examined on admission, the head was greatly enlarged its circumference measuring 66 cm. (normal average 48·5 cm.) and the anterior fontanelle was still patent. The fundi were not seen; the pupils were dilated, the right being the larger; they reacted to light although the child appeared to be blind. There was a severe spastic left hemiparesis, with an increase of the tendon reflexes and an extensor plantar response on that side. The tendon reflexes of the right arm could not be obtained, but they were normally active in the right leg and the right plantar response was indefinite; the abdominal reflexes were all present and equal. Mental development appeared normal. The child was healthy in other respects, and was not pyrexial. Lumbar puncture yielded a slightly turbid straw-coloured fluid under a pressure of 150 mm. containing no excess of white cells, but many red cells, and 25 mg. per cent. of total protein. It gave a negative Wassermann reaction. The right lateral ventricle was tapped and a similar fluid was obtained under a pressure of 140 to 150 mm. Indigo carmine (6 c.c.) injected into this ventricle was not recovered by lumbar puncture either 6 minutes or 24 hours later. The child subsequently developed further screaming attacks, and died on December 14 after being unconscious for 24 hours.

Summary of necropsy (P.M. 498. 1934).—Symmetrical expansion of skull (64 cm. circumference; 45 cm. between external auditory meati), greatest in fronto-temporal regions. Considerable convolutional atrophy of vault (maximum thickness 0·15 cm.). Anterior fontanelle 6·5 cm. wide and up to 3 cm. antero-posteriorly. Expansion of sella turcica 2·7 cm. wide; 0·4 cm. deep, and 1·2 cm. antero-posteriorly. Middle ears dry. Slight emphysema of lungs. Parenchymatous degeneration of liver and kidneys. Central softening of suprarenal bodies. Mucous catarrh of stomach and of intestines. Congestion and œdema of spleen. Caries of milk teeth. A moderately developed child.

Macroscopic examination of brain.—There was conspicuous golden-brown pigmentation of the leptomeninges over the ventral aspect of the cerebellum extending along its antero-lateral borders and over the vermis to the quadrigeminal plate. Similar diffuse pigmentation was also present over the olfactory tracts, mesial aspects of the temporal poles and to a less extent in the Sylvian fissures. A little purulent exudate was present over the antero-lateral borders of the cerebellum and about the optic chiasm. A little purulent exudate also occupied the thickened leptomeninges over the brain-stem. The fourth ventricle and Sylvian aqueduct were moderately dilated, the latter measuring 0·35 by 0·2 cm. The third and lateral ventricles were greatly dilated, the foramina of Monro measuring 1·5 by 1·0 cm. on both sides. The septum pellucidum showed marked fenestration. There was diffuse orange pigmentation of the choroid plexuses. In the right lateral ventricle in the parieto-occipital region was a triangular orifice, measuring about 4 by 3 cm., which communicated with an extensive diverticulum forming a shallow compartment over its dorsal and lateral aspects (fig. 6). The diverticulum extended forwards beneath the Rolandic fissure to within 1·3 cm. of the frontal pole and slightly overlapped the mesial aspect of the ventricle in the posterior frontal region. In the latter area it was subdivided into a few secondary diverticula by laminæ of white matter. The diverticulum extended ventrally into the dorsal border of the lenticular nucleus, while at the coronal level of the Rolandic fissure an area of softening, about 0·5 cm. in diameter, was identified in the adjacent internal capsule. The

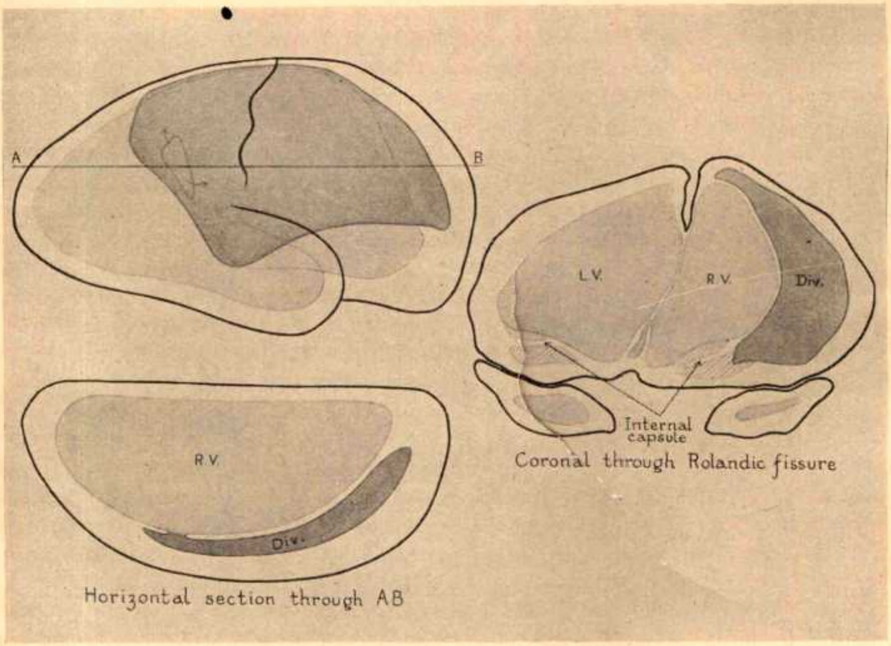

A
B
L.V.
R.V.
Div.
Internal capsule
Coronal through Rolandic fissure
R.V.
Div.
Horizontal section through AB

FIG. 6.—*Case* 2. Diagrams to show relations of diverticulum to right lateral ventricle.

septum between the ventricle and the diverticulum was everywhere composed of white matter from 0·05 to 0·1 cm. thick.

Microscopic examination.—The appearances differed only in degree from those in Case 1. Thus the leptomeninges were more intensely infiltrated with neutrophil leucocytes and with macrophages containing iron pigment. The destruction of neurones and gliosis of the cerebellar cortex at the summits of the folia were more conspicuous than in Case 1. Collections of foam cells were more numerous in the neuroglia lining the diverticulum: in a section through the basal ganglia to include the lower angle of the diverticulum these cells formed a conspicuous group surrounded by dense gliosis, corresponding to the area of softening observed macroscopically in the internal capsule. Again, in Loyez preparations there was more evidence of the active stages of myelin destruction in the walls of the diverticulum than in Case 1. Similarly sections through the mid-brain and medulla oblongata showed a definite but less advanced degeneration of the right pyramidal tract, many foam-cells and globules of myelin being present.

DISCUSSION.

In each of these cases hydrocephalus was self-evident, but the presence of hemiplegia proved to be a most misleading factor in diagnosis. In the first case the false diagnosis of a right occipital tumour was supported by the misinterpretation of the ventriculograms. In actual fact these gave an accurate rendering of the condition found at necropsy, for the air filled the diverticulum while the hinder part of the adjacent ventricle remained comparatively full of fluid. In the lateral projection the unexplained oblique shadow is th[illegible]tum between the diverticulum and the ventricle. Greater significance sh[illegible]tached to the absence of any lateral displacement of mid-li[illegible]ering the possibility of a tumour. Even so, w[illegible]complication of hydrocephalus, a co[illegible] part. In the first case the child sustained an injury to the right side of the head when he was about three years old, at which time he was known to have a large head. It was shortly after this that he developed a symptom of possible lateralising value, namely, the tendency to hold any book or picture towards the right side, which was presumably due to difficulty in looking to the left. The injury was sufficient to raise a bruise in the scalp and may also have been responsible for a breach in the adjacent ependyma. In the second case the two attacks of " screaming " were doubtless due to phases of acute internal hydrocephalus. It was after the second of these that hemiplegia developed, suggesting that the ependyma had given way before the pressure of the intraventricular fluid. Histologically, the stage of degeneration reached in the affected pyramidal tracts agrees with the clinical histories, being much less advanced in Case 2 than in Case 1, where the loss of myelin is complete.

The observation of degeneration and gliosis of the cerebellar cortex at the summits of the folia is a side-issue which will not be discussed beyond stating that we have so far found no evidence that these changes are attributable to pressure alone; it appears more likely that they are a result of chronic inflammation. Further investigation is needed to settle this point.

We have been unable so far to find any records of closely comparable cases in the literature. But in his second lecture on " Rest and Pain " Hilton describes, in an infant with internal [illegible]alus, the symmetrical division of each lateral ventric[illegible]d lower part " by an opaque structure (resem[illegible]in which there was on ea[illegible] an [illegible] in diameter." He [illegible] within the ventri-

THE ABNORMAL CORTICAL POTENTIALS ASSOCIATED WITH HIGH INTRACRANIAL PRESSURE.[1]

BY DENIS WILLIAMS

(From the National Hospital, Queen Square, London.)

WHEN studying the electro-encephalogram of patients who had mental symptoms associated with increased intracranial pressure Berger (1931) found abnormally slow alterations in the electrical potentials of the cortex. The patients had cerebral tumours, and he thought at that time that only neoplasms which had caused a sufficiently high intracranial pressure to alter consciousness would modify the electro-encephalogram. He used needle electrodes placed on the forehead and occiput and described waves of 5 to 7 a second which he said were due to slowing of the normal 8 to 12 a second "alpha" waves. Walter (1937) found slower, three a second, waves over the whole cortex and observed that there seemed to be no correlation between the height of the cerebrospinal fluid pressure and the amount of abnormality in the cortical potentials. Abnormally slow changes in cortical potentials, similar to those seen in high intracranial pressure, have also been found in cases with discrete or diffuse cerebral lesions, in the psychoses, in epilepsy, during surgical anæsthesia, and in coma from other causes. These slow waves seem to occur in cortex which has been damaged but not destroyed. They are not specific for any pathological process, but are evidence of cortical abnormality and their presence is usually related to clinical signs of cerebral dysfunction.

Clinical experience indicates that there may be little correlation between the height of abnormal intracranial pressure and its effect on the patient, for all states of consciousness from normal to profound coma are found in different subjects with similar abnormal levels of cerebrospinal fluid pressure. How high intracranial pressure causes such effects as nausea, headache, and somnolence is unknown, and the variability of its symptoms is unexplained. As its effect on the electro-encephalogram shows similar

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[1] This investigation was carried out while holding a research grant at the National Hospital. Preliminary observations were made in the Department of Neurology of Harvard University in the Boston City Hospital while holding a Rockefeller Travelling Fellowship in Neurology.

variability an investigation of the mechanisms producing the electrical slow rhythms in cases with high intracranial pressure might elucidate the physiological changes causing unconsciousness and might explain the lack of correlation between the pressure and its effects. It is the purpose of this paper to describe such an investigation in man and to discuss the significance of the results obtained.

METHODS.

The subjects used were patients in the National Hospital, Queen Square, and in the Boston City Hospital. The records were obtained through the intact skull by means of electrodes placed on the scalp. For short investigations saline pads were used, and for experiments lasting over many hours small solder pledgets were fixed to the scalp with collodion, contact being made with zinc sulphate jelly. Three active electrodes were placed on the scalp with a reference electrode over the mastoid process on the ear. The electrodes and the method of placing have already been described. (Williams and Gibbs, 1939.)

Three independent condensor-coupled amplifiers with a balanced input circuit in the pre-amplifier stage and ink-writing oscillographs were used. The systems were capable of undistorted recording of frequencies ranging from a half to seventy oscillations a second. I am grateful to A. M. Grass for their construction. The electrode placing, amplification and frequency characteristics were as far as possible similar in all the cases studied, and no change was made during the course of single experiments.

The subjects, to whom the procedure had been explained, sat or lay comfortably with the eyes closed, and the clinical state and any changes produced by the experimental procedure were noted. Cerebrospinal fluid pressure was measured in the lumbar sac in all cases with the subject recumbent. Although this does not give an absolute reading of intracranial pressure in cases of cerebral tumours (Smyth and Henderson, 1938) the error is small enough to be of no significance in the present results A 2 mm. manometer with extensions was attached to a Greenfield needle and three-way tap, readings being taken shortly before or after the investigations. When the pressure was altered experimentally, the needle was left in situ and readings taken throughout the experiment. The clinical history was used to judge the duration of the high intracranial pressure.

I am indebted to the physicians who allowed me to investigate their cases, and to the resident staffs for their co-operation.

RESULTS.

Material.—Forty-two subjects were used. The cerebrospinal fluid pressures ranged from 180 to 650 mm. of water. In nine cases with pressures over 300 mm. of water where an absolute reading had not been obtained, it was taken for statistical purposes as 300 mm. On this basis, the average pressure in the forty-two subjects was 320 mm. The distribution of cases in pressure groups is shown in Table I.

The duration of high intracranial pressure varied from thirty minutes to approximately seven years, most of the patients having had headache, nausea, vomiting or ocular signs for one to twelve months.

The causal lesions were as follows:—

Supratentorial lesions: Fifteen gliomata, eight meningiomata, three other neoplasms, two abscesses, and one subdural hæmatoma.

Infratentorial lesions: Eight tumours causing internal hydrocephalus.

Diffuse lesions causing high pressure: One case each of Paget's disease of the skull and otitic hydrocephalus, and three cases with high pressure without signs of local disease.

TABLE I.

Pressure (mm. H_2O)	200–300	300–400	300–400	400–500	500–600	600–700
Number of cases	5	15	14	4	3	1
0 = alert	0	0	0	0	++	++
+ = slow	0	0	0	0	+++	
++ = drowsy	0	0	0	0	+++	
+++ = coma	+	0	0	++		
		0	0			
		0	0			
		0	+			
		0	+			
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EFFECTS OF HIGH CEREBROSPINAL FLUID PRESSURE.

The effect of high intracranial pressure upon consciousness cannot be expressed in exact terms, for not only is the degree of impairment of consciousness variable and difficult to assess, but there are many important contributory causes, such as the position, size and nature of the causal lesion. An attempt to correlate the degree of impairment of consciousness with the cerebrospinal fluid pressure in this series of cases is shown in Table I. The state of consciousness has been arbitrarily divided under four headings, normal, obvious mental slowness or confusion, drowsiness, and deep coma. The cerebrospinal fluid pressure has been divided into groups of 100 mm. of water.

It can be seen from this table that although very high pressures were associated with marked changes in consciousness there was a very wide variation in each pressure group. This lack of correlation between intracranial pressure and its effects is well illustrated by cases with high intracranial venous pressure, caused by congestive heart failure, obstruction of the superior vena cava, and Ayerza's disease (Ferris, 1939). In these cases very high intracranial pressure of long standing is usually unassociated with any of its usual concomitants—headache, nausea, vomiting, and changes in consciousness.

It is impossible to compare the degree of abnormality in the electro-encephalogram in a group of subjects, for the frequency, amplitude and number of abnormal waves must be considered, and each of these factors may vary independently (fig. 1). More accurate observations may be made by comparing changes in individual records as the pressure is altered (fig. 2). A constant relationship between the height of pressure and the degree of abnormality in cortical potentials was not found in this series of cases. In general an increase in cerebrospinal fluid pressure was associated with some abnormality, which was most marked in subjects with very high pressure. Only three records in the series were considered normal. These were from patients with cerebrospinal fluid pressures of 410, 290 and 270 mm. of water.

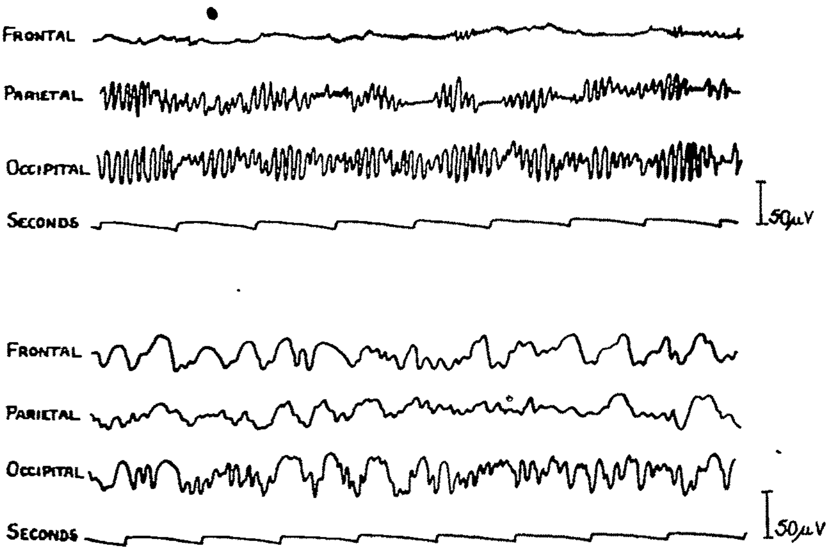

FIG. 1.—Tracings from electro-encephalograms obtained with paired leads from the frontal, parietal and parieto-occipital regions of the skull of two subjects

The upper is from a normal subject, a well-sustained rhythm of nine a second being present in the parietal and occipital leads. The lower is from a patient who had an internal hydrocephalus with a cerebrospinal fluid pressure of over 300 mm. of water. High voltage waves of one to two per second are present in all leads. They are most evident in the frontal region and have a superimposed rhythm of nine a second in the parieto-occipital leads. The slow waves have the same phase relationships in all leads.

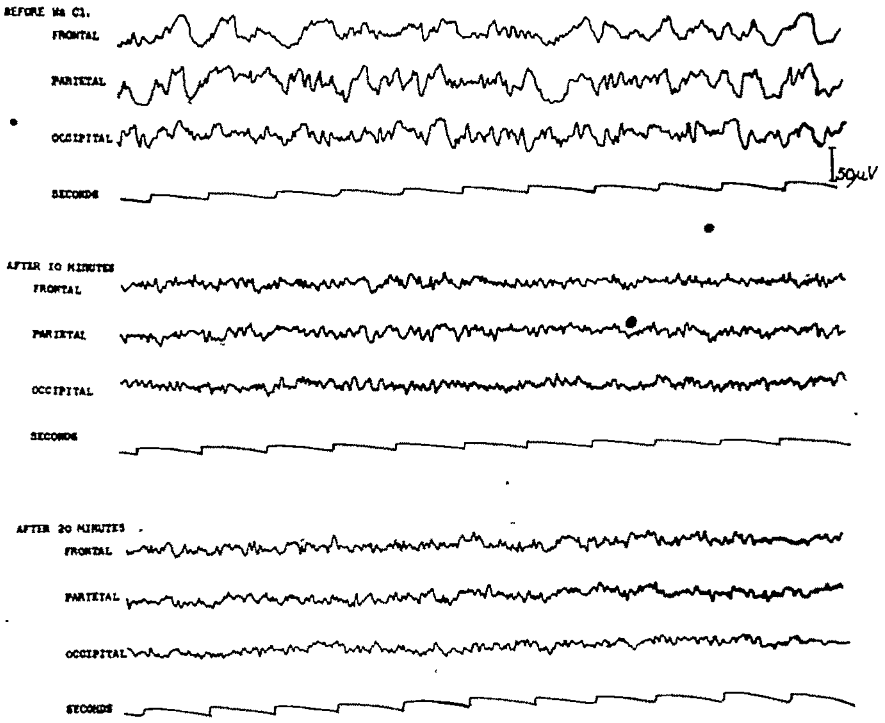

FIG. 2.—The electroencephalogram of a subject with an intracranial pressure of 340 mm. of water, due to a posterior fossa tumour. The electrode placing and amplification were constant throughout. The top records were obtained immediately before an intravenous injection of 45 c.c. of 30 per cent. sodium chloride. Ten minutes later the pressure was 110 mm. of water, and twenty minutes after the injection it was 120 mm. There is almost complete disappearance of the abnormal slow potentials. These results are expressed numerically in fig. 4.

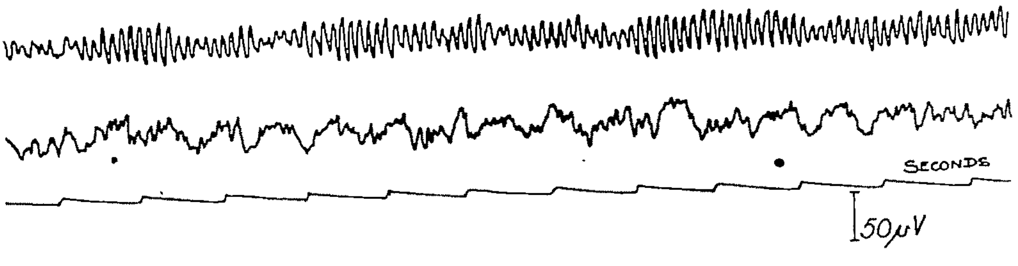

FIG. 3.—Records obtained under similar conditions from the parieto-occipital regions of two subjects. The upper, from a patient with an intracranial pressure of 410 mm. of water, shows a well-sustained normal rhythm of nine to ten per second. The lower, from a subject whose intracranial pressure was 430 mm., shows a sustained frequency of one and a half per second, with a superimposed faster rhythm.

It is true that the criteria of normality are difficult to assess, but frequencies of less than four or five per second were usual in this series, and are exceptional in large groups of normal subjects.

Fig. 3 shows the potentials taken under similar conditions from similar cortical areas in two different subjects. Both had an intracranial pressure of long standing between 400 and 450 mm. of water. While the lower record shows a well-sustained rhythm of 10 per second, the upper has a similar rhythm superimposed on a slower-sustained rhythm of 1 to 2 per second. These slow waves constitute the characteristic abnormality under discussion.

Lastly, in comparing changes in consciousness with alterations in cortical potentials, abnormal slow potential changes were invariably found throughout the cortex in subjects with marked impairment of consciousness, but similar abnormalities were also seen in subjects appearing mentally normal. Increasing depth of coma appears to be associated with an increase in voltage of the slow waves, as noticed by Walter (1939). Although less than half the present cases showed any impairment of consciousness only three had normal cortical potentials. The other thirty-nine showed waves the size and periodicity of which were well outside the widest limits of the normal. Impairment of consciousness is therefore not essential, as Berger (1931) thought, to the occurrence of abnormal cortical frequencies with high intracranial pressure.

The abnormal waves associated with high intracranial pressure have several constant features. They are widespread over the cortex, are extremely rhythmic and well-sustained, and are very slow, the more evident frequencies being two per second and less, in contrast to the abnormal waves around tumours, which are much more variable and are usually faster than this. Waves very similar to those seen in cases with high intracranial pressure are seen in the vicinity of cerebral abscesses, but they most closely resemble the slow rhythms of relatively low voltage seen in coma of all types. When high pressure is associated with coma the waves are indistinguishable from those seen in unconsciousness resulting from other causes.

The voltage of the slow waves varies from zero to 100 microvolts, being usually about 50 microvolts, the amplitude being roughly associated with the clinical effects of pressure. They appear to increase in amplitude with little alteration in the normal dominant frequency, which may continue uninterrupted (fig. 3). Gibbs, Williams and Gibbs (1939) showed that slowing of all frequencies may result from experimental alteration in blood constituents. Although the exact method of analysis of wave lengths which they used was not available in this present work, it seemed that there was little slowing in normal frequencies in most cases with high pressure. The main abnormality was an increase in the voltage of the slower waves which if present in normal subjects are so small as to be completely masked by the faster frequencies.

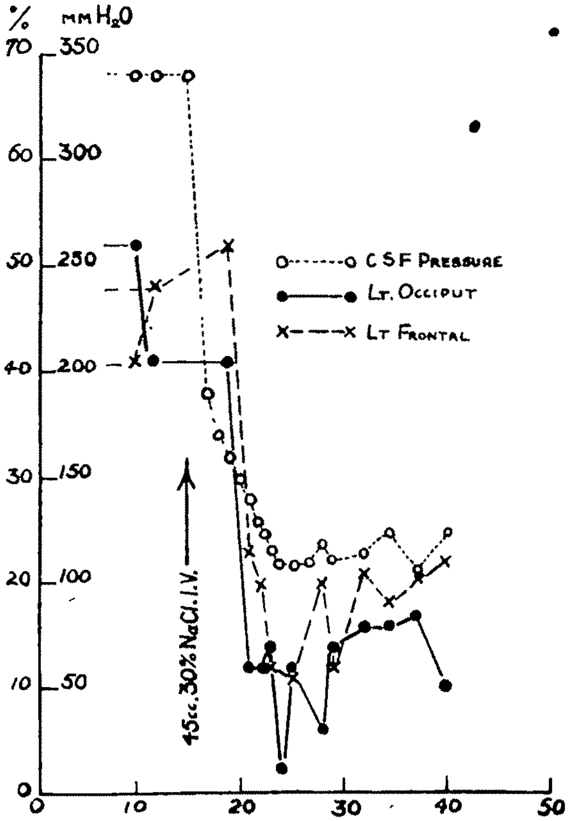

FIG. 4.—A graph showing the effect of 45 c.c. of 30 per cent. sodium chloride on the cerebrospinal fluid pressure and electroencephalogram of the subject whose record is illustrated in fig. 2. In this and succeeding figures the abscissæ represent time in minutes and the ordinates the percentage of time in a given length of record occupied by abnormally slow waves of cortical potential, with cerebrospinal fluid pressure in mm. H_2O.

The slow potential changes show a constant pattern throughout the cortex. With similar records from four points on each hemisphere, using paired electrodes in linear arrangement, their phases are simultaneous and of like sign, all points on the cortex becoming positive or negative simultaneously. The absence of any evidence of spread from one part of the cortex to another suggests a central oscillating mechanism, propagating the disturbance uniformly to the surface of the hemispheres.

EXPERIMENTAL MODIFICATION OF CEREBROSPINAL FLUID PRESSURE

In a series of experiments on selected cases the cerebrospinal fluid pressure was lowered by means of intravenous injections of hypertonic

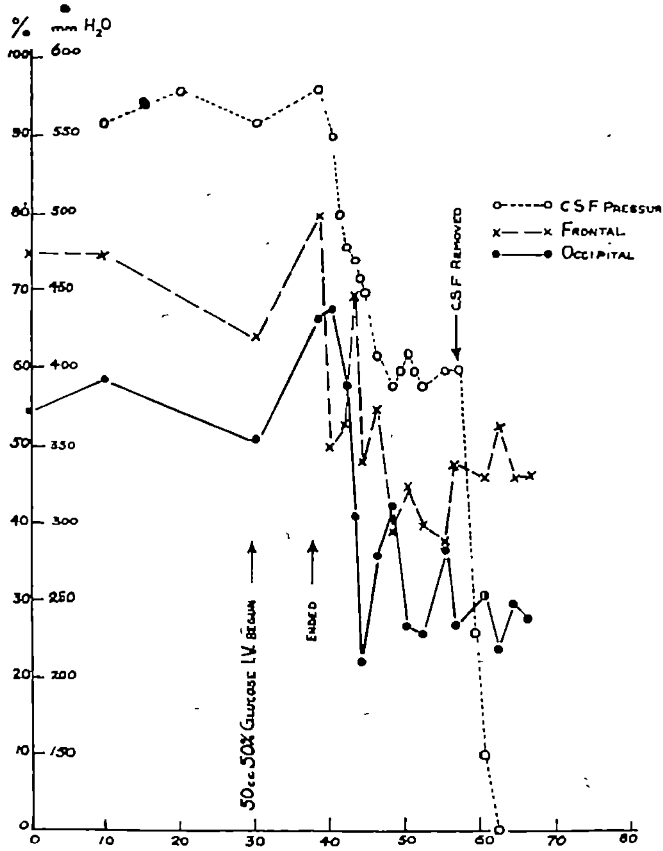

FIG. 5.—The effect of intravenous injection of 50 c.c. of 50 per cent. glucose on the cerebrospinal fluid pressure and electroencephalogram of a patient with otitic hydrocephalus and an initial pressure of 550 mm. of water. Records were obtained from the frontal and occipital regions of the same side of the skull. The cerebrospinal fluid was finally removed by drainage as a therapeutic measure.

solutions—glucose, sucrose, and sodium chloride—and by simple removal of cerebrospinal fluid. In one subject with otitic hydrocephalus treatment involved repeated drainage of cerebrospinal fluid. A series of different experiments were therefore carried out in this subject.

Fig. 2 shows the effect of intravenous injection of 45 c.c. of 30 per cent. NaCl on the cortical potentials of a patient with an initial cerebrospinal fluid pressure of 340 mm. of water. It will be seen from the complexity of the record that the comparison of subjects would necessarily involve much subjective interpretation of the data. To overcome this difficulty numerical indices of normality and abnormality have been used by other workers. Dietsch (1932) carried out a true Fourier transform, and Hoagland (1937) expressed the size and number of abnormal slow waves in an index, the "delta index." The most accurate and practical method is that of Gibbs and Grass (1938) who plotted frequency against energy, using an electric frequency analyser. For the present study a simple and adequate index of abnormality is the proportion of time occupied by frequencies of three a second and less in a known length of record. This index is obviously crude and does not consider amplitude, but comparison with detailed examination of the records shows that it is adequate for the present purpose, and it enables the changes to be plotted against cerebrospinal fluid pressure (fig. 4). The method was standard in all cases.

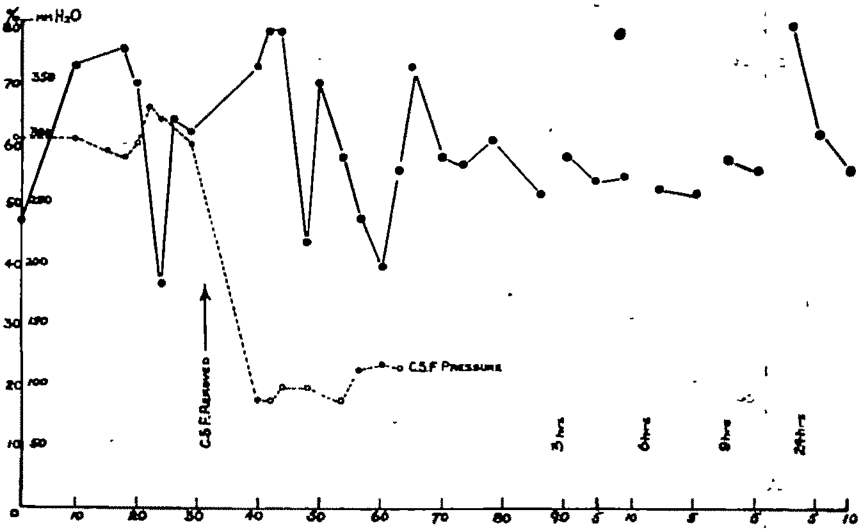

FIG. 6.—The effect of lumbar drainage of cerebrospinal fluid upon the electro-encephalogram from the parieto-occipital region of a patient with otitic hydrocephalus. A continuous record was obtained for an hour, and samples were then taken three, six, nine and twenty-four hours afterwards.

An intravenous injection of 30 to 50 c.c. of 50 per cent. glucose in normal saline was given in seven cases with supratentorial tumours, obstructive hydrocephalus and toxic hydrocephalus. The cortical potentials became practically normal in all cases within ten minutes of completing the injection (fig. 5). Injection of 50 per cent. sucrose gave a result similar to that obtained with glucose. The responses to intravenous injections of 50 c.c. of 50 per cent. glucose and to 40 c.c. of 30 per cent. NaCl in four

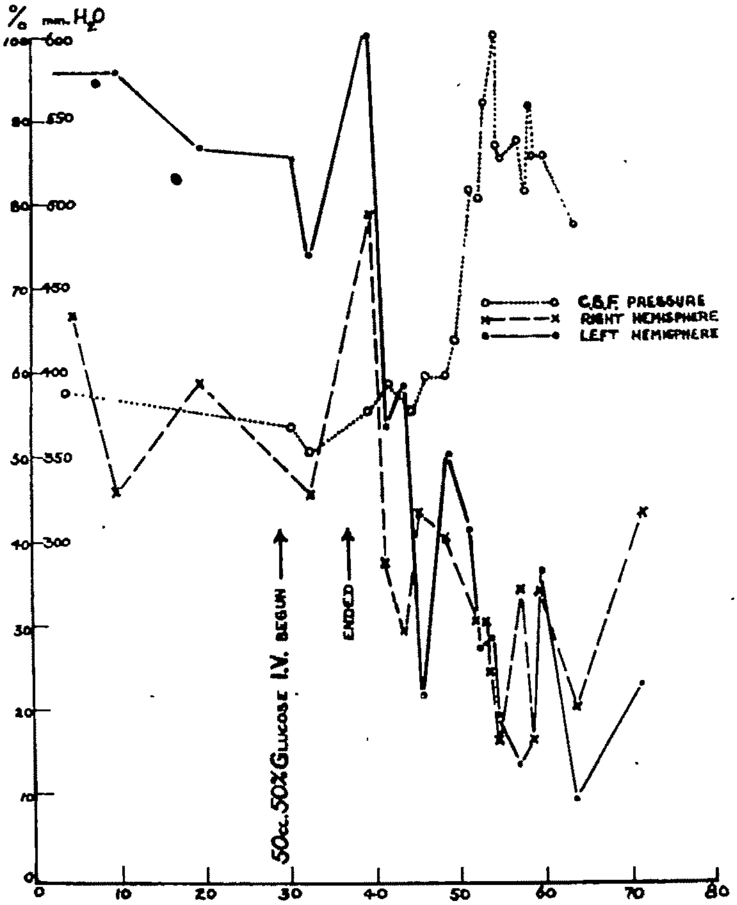

Fig. 7.—The effect of intravenous injection of 50 c.c. of 50 per cent. glucose on the cerebrospinal fluid pressure and the electroencephalogram of a subject with a large infiltrating glioma of the right frontal lobe. There is no change in the cerebrospinal fluid pressure for twenty minutes after the injection. There is then a rise from 400 to 600 mm. of water. The alteration in the electroencephalogram from both hemispheres bears no relationship to the change in intracranial pressure, but the curve is similar to that seen in figs. 4 and 5.

similar cases were identical, except that NaCl was more rapid in its effect (figs. 4 and 5). Removal of cerebrospinal fluid by drainage was without effect in three experiments on two cases, during the period immediately after removal and for periods up to three days afterwards (fig. 6).

There was no relationship between the alteration in the electroencephalogram and the concomitant fall in cerebrospinal fluid pressure. One subject with a large right frontal glioma had generalized abnormal waves with a pressure of 390 mm. Intravenous injection of 50 c.c. of 50 per cent. glucose did not alter the intracranial pressure, but reduced the time in the record occupied by abnormal cortical potentials to less than half, within ten minutes (fig. 7). Twenty minutes after the injection of glucose there was a rapid reaction causing the cerebrospinal fluid pressure to rise to 600 mm. of water. The record remained in its improved state, but thirty minutes after the injection when the effect of the hypertonic glucose was decreasing the pressure began to fall and the abnormal potentials began to reappear.

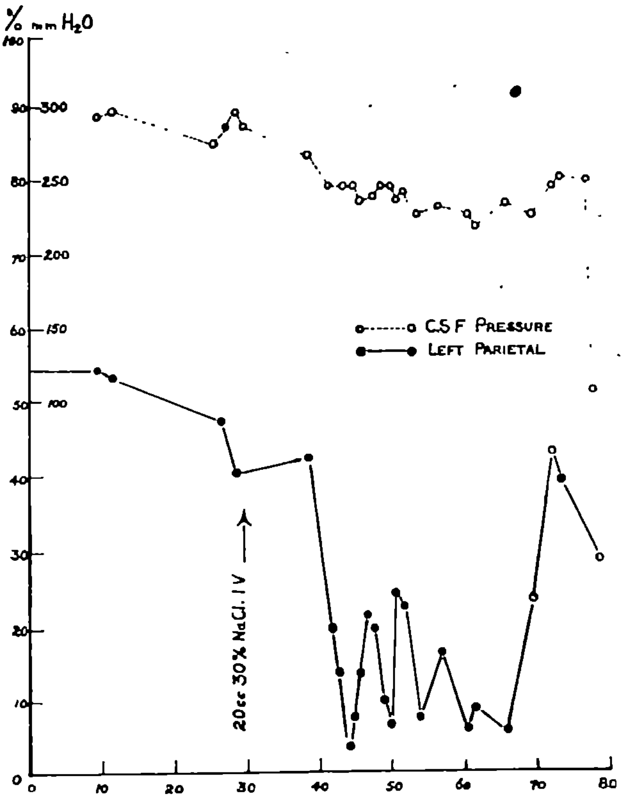

FIG. 8.—The effect of intravenous injections of 20 c.c. of 30 per cent sodium chloride on the abnormal electroencephalogram of a subject with otitic hydrocephalus, in the absence of any significant change in the cerebrospinal fluid pressure.

In two normal subjects the cerebrospinal fluid pressure was maintained for thirty minutes in the region of 500 mm. of water by means of a sphygmomanometer cuff placed around the neck with two pads over the jugular veins. A pressure of 30 mm. of mercury was used, with no discomfort to the patients. There was no change in the electro-encephalogram.

Two subjects with normal cerebrospinal fluid pressures and normal cortical potentials were given a subcutaneous injection of ½ c.c. of pitressin. During the next three hours six pints of fluid were taken. In one case the cerebrospinal fluid pressure rose from 70 to 190 mm. of water, diuresis occurring after nine hours, and in the other it rose from 120 to 280 mm. with diuresis after seven hours. An abnormal pressure was therefore maintained for over six hours in each case. Electro-encephalograms repeated at intervals for twenty-four hours before and after the rise in cerebrospinal fluid pressure did not show any significant alteration.

Two cases had had high intracranial pressure many years previously. The pressure had been relieved by surgical decompression, and there had been no evidence of abnormal pressure for five and twelve years. In both these cases there had been no supratentorial lesion, and the decompression openings were soft and flat. Clinically the only sequel to the longstanding high pressure was consecutive optic atrophy. Both subjects showed abnormal, slow potentials over the hemispheres. Thus, although it has been shown experimentally that the mechanism causing slow waves is reversible, it may remain irreversible in some conditions.

DISCUSSION.

These results show that the slow waves of cortical potential associated with abnormally high intracranial pressure are not directly due to the pressure. They are modified by intravenous injection of hypertonic solutions in the absence of any pressure change, so that they must depend primarily on an alteration in water balance or ionic concentrations in the tissues. Widely different molecules in hypertonic solutions gave similar results, so that the change causing slow potentials with high cerebrospinal fluid pressure must be an abnormal water retention, that is œdema, and not a disturbance of specific ions.

The potentials originate in the neighbourhood of cortical cells (Dusser de Barenne and McCullough, 1936), but they may be modified by changes remote from the cell bodies, for Bishop (1936) produced similar slow waves from normal cortex by section of the underlying white matter. The change in water balance producing the slow rhythms with high cerebrospinal fluid pressure, therefore, may be either in the grey matter or in the underlying fibre masses. Jaburek (1935) and, later, Greenfield (1939) found that an œdematous change confined to the white matter occurs in association with cerebral tumours. The areas of œdema show secondary neuronal changes and may extend to some distance from the tumour.

Stewart-Wallace (1939) has determined the sodium, potassium, chloride and water content of the grey and white matter in conditions in which general or local cerebral œdema is present. He finds that œdema is almost entirely confined to white matter. Circumscribed deep tumours without high intracranial pressure or change in consciousness cause low voltage slow waves in the overlying cortex. As these slow potential waves arise from the cortex as a result of damage to white matter it is probable that the changes in the electro-encephalogram seen with high intracranial pressure are due to alterations in the water content of the white matter and not of the cortex itself. Further evidence in support of this is the unpublished observation of Greenfield (1939) that areas of demyelination, similar to those which he has described around tumours, occur in cases of uncomplicated internal hydrocephalus. The results of an investigation into the water content of the white matter in these cases will be of extreme interest.

In the present experiments, the duration of high cerebrospinal fluid pressure following pitressin may not have been adequate to produce the slow potential changes. The water retention resulting from injection of the pituitary extract is, however, always extra-cellular. The abnormal rhythms produced by high pressure may be due to œdema within the substance of the cell processes. If this were so, the negative results of high cerebrospinal fluid pressure following water retention with pitressin would then be explained.

This negative result after seven hours of high intracranial pressure has further importance, for it excludes cerebral anoxia and cerebral anæmia, which have been evoked to explain the effects of high intracranial pressure. Lenox, Gibbs and Gibbs (1938) have shown that the effects of cerebral anoxia on cortical potentials occur extremely rapidly below a critical threshold, above which the potentials remain normal. Further, Williams and Lennox (1939) have shown that high intracranial pressure is not associated with changes in total cerebral blood flow, so that circulatory changes can be excluded.

Griffiths, Nevin and Walter (1939) found generalized abnormally slow potential changes in a patient who had a tumour of the hypothalamus, and who was in deep coma. The cortex and underlying white matter were normal, so that the abnormally slow waves may have been produced by damage to secondary neurones. This raises the possibility that a state of abnormal cortical activity may be maintained by trans-synaptic conduction of a remote disturbance. The physiological interruption of cerebral pathways resulting from œdema of white matter might, therefore, cause the widespread physical change described in this paper. Such alterations in the normal electrical activity of the cerebral cortex are the usual accompaniments of coma, and are probably a manifestation of the underlying cause of the changes in consciousness resulting from uncomplicated high cerebrospinal fluid pressure. It would then be unnecessary to evoke such complicated mechanisms as medullary, mesencephalic, or hypothalamic distortion or ischæmia by pressure cones as causes for the changes in behaviour resulting from high intracranial pressure.

SUMMARY.

The changes in cortical electric potentials in patients with abnormally high intracranial pressure have been studied in relation to the clinical state and the height and duration of the abnormal pressure. There was little correlation between the pressure and its effects on the state of consciousness of the subject and on the changes seen in the electroencephalogram.

Experimental modification of cerebrospinal fluid pressure showed that the abnormal waves of electrical potential were due to secondary osmotic changes in the cerebral tissues. Evidence has been produced that this change is probably an œdema of the nerve fibres in the white matter of the hemispheres.

The underlying mechanisms causing the changes in cortical electrical activity and in consciousness have been discussed.

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NOTICES OF RECENT PUBLICATIONS.

The Organism. By KURT GOLDSTEIN. New York: American Book Company. 1939. Pp. 533. Price 4 dollars.

This work first appeared in German in 1934, and the present book purports to be an English translation thereof. The nature of the problems discussed and the qualities of the exposition would have made translation a task of extreme difficulty even for one whose native tongue was English. The recurrence in the book of words that are not known in English (such, for example, as "valence," "innerness," "pregnanz," "motoric," "envision," and the like) as well as the prevalence of German linguistic constructions suggest that the translator is himself not at home in our language.

Goldstein seeks to apply the doctrine of Holism to the study of the living organism, and being a neurologist he has not unnaturally chosen the nervous system to exemplify and illustrate his theme. The nervous system, which he speaks of as a network, functions always as a whole and never in part. Even the simplest "performance" of the organism demands this comprehensive activity. Underlying the "performance" is the "foreground process" in the nervous system, and associated with this is a "background process" consisting in an adjusted reaction of the rest of the nervous system not actually engaged in the foreground process.

This doctrine is not wholly unfamiliar and in principle is valid enough, though at times it leads the author to overstatement, as when he says that "each movement of one part of the body is accompanied by a definite change in the posture of the rest of the body." It would be easy to cite examples in which, whatever the activity within the nervous system, a simple movement has not this extensive result, e.g. in that familiar communicating gesture of the eyelid known as a "wink."

The prime end of the organism is said to be "to come to terms with the environment," and to this end structure and function combine: thus "the structure of any organism is such that it makes possible performances which are the fulfilments of the requirements of its environment," a statement that is readily seen to be a *petitio principii,* a form of logical fallacy of which other examples are to be found in the book.

The author postulates certain laws of "disintegration" of function resulting from cortical lesions, that will interest those familiar with Jackson's doctrine of dissolution of function within the nervous system to which they bear certain resemblances, though Goldstein has not penetrated so deeply into this problem as his predecessor. Thus, he states that: (*i*) in a specific field of performance (e.g. visual, motor) a single performance never drops out alone, all performances in the field are affected; (*ii*) a single performance does not drop out completely. Some individual performances persist; (*iii*) in all performances the modifications affected by disease obey the same laws. These modifications are spoken of in general as "change in behaviour"; (*iv*) isolated movements are more affected than integrated movements, complex movements more than simple movements; (*v*) the organism tends to optimal performance, and when damaged achieves this by "functional shift" and by substitute performance; (*vi*) the behaviour of the intact organism is "ordered": that is, constant, consistent and adequate, that of the damaged organism is "catastrophic," that is, inconsistent, inconstant and inadequate and "embedded in physical and mental shock"; (*vii*) the damaged organism has a restricted environment and seeks to avoid catastrophic reactions by maintaining a "primitive order" within this. It does this by incessant simple activities of a kind within its now limited capacity.

The author then proceeds to a vigorous attack on what he calls "reflexology." This includes an objection even to the term "reflex action," though how the substitution of "performance" for this achieves an advance in knowledge is not easy to discern. He objects, also, to the methods by which in experimental animals the reflex action has been studied, though elsewhere he has to admit that it is only by this scientific, analytic "anatomizing" method that knowledge can be gleaned, since the naive inspection of performances is inadequate. He objects, too, to the physiologists' preoccupation with the lower animals, though in refuting the "useless concept" of inhibition he does not hesitate to cite some experiments of Bethe on annelids.

Much of his criticism of the physiology of reflex action appears based upon imperfect acquaintance. Thus, he protests that reciprocal innervation cannot apply to voluntary movement, but appears unaware that it has never been supposed to do so, and that the notion of double reciprocal innervation has already disposed of what there is of substance in his objection. This crude misrepresentation of reciprocal innervation seems to have as many lives as a cat, and is constantly appearing in clinical neurological literature, though it is an error that could not survive any serious study of Sherrington's work, particularly of his paper entitled "Reflex Inhibition as a Factor in the Co-ordination of Movements and Postures." (*Quart. Journ Physiol.*, 1913, 6, 251.)

In fact, the "reflexology" of the author is something other than the reader of Sherrington's Rede Lecture understands: it is largely a figment of the author's mind Thus, he supposes it to regard the organism as "a bundle of isolable mechanisms" and the life of the organism as simply the sum of these "disparate mechanisms" wholly lacking in that regulation and direction we know the organism to possess.

Yet in J. S. Haldane's Silliman Lecture in 1915, entitled "Organism and Environment as illustrated by the Physiology of Breathing," we have a penetrating exposition of Holism—though not so named—close upon a quarter of a century old, an exposition which, as its author clearly showed, in no way involves an abandonment of the notion of reflex action.

In rejecting both the doctrines and the precise nomenclature of physiology the author has had perforce to deal with his problem in intellectual isolation, and by the use of clumsy *ad hoc* locutions. He has burdened his exposition with highly equivocal terms; thus in a single paragraph the word "perception" appears as meaning both the act of perceiving and the thing perceived. We may not speak of "facilitation," but of the "tuning of the substratum gained through experience," which is pure allegory. The vocabulary of scholastic philosophy is drawn upon and we read that the tasks of the organism are determined by its "essence" which "is brought into actualization through the environmental changes that act upon it"

Nor can it be said that these strange mediæval figures, "being," "essence" and "nature" impart clarity to the sentences in which they appear so incongruously.

Since Jackson's time we have had no broad generalizations in the field of clinical neurology, and the many additions to our information in the last century call for generalization and synthesis. Here and there in his pages the author gives indications that he has valuable notions to impart, but an attempt at synthesis that rejects the physiology of reflex action, a body of knowledge so firmly and so precisely founded, and ignores those notions of cortical localization and of dissolution of function given us by Jackson cannot hope for success, and, in fact—for all its interest—this book represents a synthesis "manqué."

Annual Review of Physiology. Edited by J. M. LUCK and V. E. HALL. Vol. I. Published by the American Physiological Society and Annual Reviews Inc., Stanfard University, P.O., Cal. 1939. Pp. 705. Price 5 dollars.

This, the first of an intended annual series, sets out to give a comprehensive review of the year's research in physiology. The general method is critical rather than that of a simple *précis*.

The whole field of physiology is covered, and the articles of special interest to the neurologist are those dealing with "The Spinal Cord and Reflex Action" by J. C. Eccles, "Electrical Phenomena of the Brain and Spinal Cord" by Hallowell Davis, and "Bioelectric Studies of the Excitation and Response of Nerve" by Bronk and Brink.

All three articles are devoted to electro-physiology, and although the clinical neurologist will wish to keep abreast with advances in this very special field, and will hope in time to receive practical assistance from them, he will view with mixed feelings this gradual recession of neurophysiology towards pure physics, and while he may console himself that biology is thus approaching fundamentals he may well wish that it was a little less remote from the world in which he has to live and labour.

A Textbook of Clinical Neurology. By I. S. WECHSLER. Fourth Edition, revised. London: W. B. Saunders Company. 1939. Pp. 844 Price 32s. 6d.

That a fourth edition should be called for indicates the value of this straightforward account of clinical neurology. As in previous editions, the emphasis is upon the clinical approach, and student and practitioner will find the book a reasonably comprehensive and a reliable statement. The author has been successful in bringing it up to date without increasing its bulk.

Science in Progress. Edited by G. A. BAITSELL. New Haven: Yale University Press. 1939. Pp. 322. Price 18s.

This volume of essays is published by the "Society of the Sigma XI," which organized the series of addresses from which the present essays have been amplified. They summarize recent research in many and diverse fields of scientific knowledge. from physics to physiology.

They vary somewhat in style, some of them being only intelligible to specialists in the fields concerned, but several of them are written in a simple and graphic style that allows the ordinary reader to follow them Such are the essays on the viruses, on vitamins and hormones, on chromosome structure, on electrical potentials in the brain, and on metabolism.

To all who wish to know what is being done in other branches of science than their own these essays will provide interesting and informative reading.

Psychotherapy: Scientific and Religious. By Marcus Gregory, with an introduction by Dr. William Brown. London: Macmillan and Co. 1939. Pp. 484. Price 21s.

In his introduction Dr. William Brown warmly recommends this book as a "sound and reliable textbook" of a subject "within the domain of medical practice": surely an odd introduction to a work written by a non-medical writer who cannot possibly deal with those problems of diagnosis that are as essential a condition of rational psychotherapy as of the treatment of physical illness. Yet this disability has no difficulties for the author, who states (p. 272): "It is said, for instance, that whereas psychological treatment may be of value in cases of functional disease, it could be of no use where there is organic derangement. But this is untenable, because the distinction between functional and organic disease cannot be carried any distance Actually, of all the diseases (*sic*) with which psychotherapists are expected to deal, those connected with the nerves are the most intractable" It would be difficult to cram more error and confusion of thought into one statement than this contains. Yet it serves its author's purpose in that it sweeps airily away the distinctions between physically and psychologically determined ill-health, makes diagnosis quite superfluous, and thus engagingly opens the entire field of healing to the lay psychotherapist. The author's pages abound in aphorisms culled from other works on psychological healing, and of the more unmeaning of these we may instance two: thus, "health has to do with a right insight, so far as it goes, into the truth of existence" and again "as error is a falling away from truth, so disease is a falling away from health." It is surely clear that whether, in these verbal exercises, we seek to find religious, philosophical or medical truth, we shall come away unsatisfied.

In short, the reader is forced to ask himself of this book "why was it written and for whom?" Neither sponsor nor author provides an answer. It can be of no value to the doctor, and it would be disastrous if its study led the lay reader to think himself fit to embark upon psychotherapy, for in the hands of the lay psychotherapist thus tutored we could look for no more than a perilous cult of treatment without diagnosis.

Experimental Psychology. By Robert S. Woodworth. London: Methuen. 1939. Pp. 889. Price 18s.

Those who are not themselves professional psychologists are apt to think of psychology as a blend of metaphysics, sensory physiology, the investigation and treatment of neuroses, and other limited or unsatisfactory studies. Much of this confusion arises from ignorance of the solid progress made in experimental or quantitative psychology, and much also from the readiness of those mainly concerned with applied psychology to depreciate scientific work in the subject as academic and sterile. An authoritative account of the methods and achievements of experimental psychology is therefore very welcome. Professor Woodworth, who has rare and indisputable qualifications for the task, has produced a most valuable compendium. He has deliberately excluded the whole field of individual differences and correlations, which can be found well enough in many other books, as well as social, genetic, educational, abnormal and applied psychology—branches still largely in the pre-scientific stage. The presentation is factual, with critical comments, and a fair statement of the present position in regard to problems of emotion, memory, perception, learning, reaction time, thinking, and other main divisions of the theme. Although the material has been in process of collection since 1910, Professor Woodworth has succeeded in including recent work from various countries (e.g. Zangwill's studies of the last three years at Cambridge find mention). A full biography and index make reference easy.

Die Gesetze des normalen Träumens. von K. Leonhard, M.D. Leipzig: Thieme. 1939. Pp. 124. Price Rm. 5.40.

From study of the records of his own dreams during several years the author has sought to discover regularly occurring relationships or "laws." He refuses to consider any of the psycho-analytic views, explaining that these are due to an "alien racial soul." It is regrettable that he has, presumably for like reasons, denied himself any acquaintance, either with the large non-psycho-analytical literature on dreams written in languages other than German. The monograph, which contains nothing new, deals first with various aspects of dreams, especially their connection with waking experience, a section on hypnagogic phenomena and those of waking up and fatigue follows, and there is a final, rather barren chapter on the theory of dreams.

Psychopathic States. By D. K. Henderson, M.D. London: Chapman and Hall. 1939. Pp. 178. Price 8s. 6d.

This series of lectures, delivered to commemorate the American psychiatrist Thomas W. Salmon, represents an essay in social medicine almost more than in psychiatry, a homily rather than a disquisition. Without attempting to classify the forms of maladjusted personality commonly grouped as psychopathic, Professor Henderson describes a number of illustrative cases, and emphasizes the connection between constitutional factors and treatment. He takes the field against one-sided psychological interpretations and ignorant optimism, but holds that with a well-planned biological approach to the problem of treatment valuable results can be attained in the social rehabilitation of these psychopaths. The lectures are lucid and balanced, with a solid foundation in experience.

Clinical Studies in Psychopathology. By H. V. Dicks, M.D. London: Edward Arnold. 1939. Pp. 248. Price 12s. 6d.

The material of this book was originally given as a series of lectures at the Tavistock Clinic, of which the author is Assistant Medical Director. There are ten chapters dealing with neuroses, sexual perversions, and drug addictions: except for a note dealing with the last of these, treatment is not directly considered. Although the writer emphasizes that his approach is eclectic, his acceptance of the Freudian system is so thorough-going and the few divergences so trifling that this book is in effect an exposition of the more extreme psycho-analytic views. Freudians will detect unintentional departures from their orthodoxy, inevitable in one who has not received their training, but to others the almost universal discovery in the cases recorded of very bizarre fantasies concerned with the sexual organs of both sexes will be reminiscent of the more florid psycho-analytical writings, and perhaps also unconvincing, if not wearisome. Any appraisal of the tenets here expounded would be almost entirely dependent on one's acceptance or rejection of the Freudian system. Dr. Dicks sets out his views clearly and well; his limitations are evident in some incidental references to other forms of mental illness than neurosis or sexual perversion, and in the general chapter which concludes the book; this is a slightly defensive plea for psychological monism, containing the startling claim that "it is probably true to say that the art of clinical observation and recording stands higher to-day among psychopathologists than in any other speciality of medicine where instruments are more and more tending to replace the human element. It is probably also true that we are on the whole more aware of the framework of reference into which our work fits within the general body of medical knowledge and investigation than our 'organic' brethren."

DECEMBER, 1939

BRAIN.

PART 4, VOL. 62.

CONGENITAL MYOTONIA IN THE GOAT.

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WE have recently been able to obtain from the United States of America a number of goats suffering from a congenital form of myotonia. A comprehensive account of what is known of their history has already appeared (Kolb, 1938), and we do not propose to discuss it in any further detail. It is sufficient to say that the similarity between this disease in goats and Thomsen's disease in man is very close, the characteristic symptom in both cases being the involuntary persistence of voluntary contraction.

There have been in the past much speculation and some experimental work on the locus of the abnormality in the human disease. The main question has been whether an abnormal discharge of motoneurones is responsible, or whether it is an abnormality of the peripheral structures, i.e. of nerve, of neuro-muscular transmission, or of muscle itself. The problem has been further complicated by the fact that there has been no clear evidence as to the precise nature of the long-lasting developments of tension, which are so characteristic of the disease. Bremer and Mage (1929), for instance, prefer to regard myotonia as a contracture, closely analogous to the " neuro-muscular contracture " which Bremer has observed in amphibian muscle. The only satisfactory criterion for discriminating between contraction and contracture is the existence in the case of a true contraction of oscillatory action potentials in association with the prolonged tension, and here instrumental errors have played some part. Many observers in the past have regarded the myotonic shortening as a contracture on account of the absence of such potential oscillations from string galvanometer records of gross muscle action potentials. Not only is the string galvanometer insufficiently fast to show certain oscillatory potentials, but, as our present work has shown, even an instrument capable of following the fastest potential variations may not reveal any definite abnormality in the diseased muscle, if the leads from the muscle are too diffuse. For instance, Eichler and Hattingberg (1938) have found the action potential of myotonic muscle to be essentially normal, and our own experiments show that it may appear to be so, when the recording electrodes are applied so as to lead from a large proportion of the muscles fibres. It is only when records taken from belly and tendon of the muscle are supplemented by a study of the activity of relatively few fibres by means of a more localized lead, such as that provided by a concentrie needle electrode, that the full electrical picture can be appreciated.

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The recent developments in the theory of neuro-muscular transmission have given more than a practical interest to investigations on the muscular disease, and the dramatic effects of eserine and its analogues in the therapy of myasthenia gravis have naturally focused attention on the neuro-muscular transmitting mechanism as a likely site of the abnormality in this condition, and by analogy, in congenital myotonia, which is in so many respects the converse of myasthenia. The fortunate provision of an animal, suffering from a congenital myopathy, has enabled us to apply to the investigation of the condition in question the ordinary methods of myographic and electromyographic examination which have proved of use in physiological and pharmacological studies. We have set out to obtain as clear evidence as possible on the following points:—

(*a*) Is the prolonged tension of a myotonic muscle due to a contracture or to a contraction proper ?

(*b*) Is it due to an abnormality of motoneurone discharge ?

(*c*) If the abnormality is peripheral, is the neuro-muscular transmitting mechanism involved ?

The information we have obtained up to the present points clearly to an abnormality of the muscle fibre itself, without any direct involvement of the neuro-muscular transmission or of the central nervous system.

A preliminary account of this investigation has appeared in the *Journal of Physiology* (Brown and Harvey, 1939).

METHODS.

The goats which we have used, normal and myotonic, have weighed between 16 and 72 kg. On account of the necessity of maintaining the breed, our myographic examinations of the myotonic goats have been confined hitherto to two animals, one a female of 21 kg., and the other a male of 23 kg. We have, as far as possible, done control experiments on normal animals of the same weight as these two.

Nembutal (sodium ethyl-l-methyl butyl barbiturate) in 10 per cent. solution has been used as the anæsthetic in all experiments. It was given intraperitoneally in doses from 0·8 to 1·2 c.c. per kg. body-weight, and anæsthesia was maintained by additional injections intravenously of 2·0 to 4·0 c.c. per hour. We used the same anæsthetic for the aseptic section of the sciatic nerve.

For the examination of the effects of substances injected at close range into the arterial system of the muscle, we have used either the gastrocnemius or the tibial group of muscles. The gastrocnemius of the goat does not provide a very satisfactory preparation, since not only is the muscle very bulky, but the dissection involved is prolonged and laborious. When the gastrocnemius was prepared we were able to use a technique in no way different from that used in the same preparation in the cat or dog (*cf.* Brown, Dale and Feldberg, 1936), and the same applies to the preparation of the soleus for simple myographic recording. The tibial group of muscles offers in the goat a better preparation, though not an ideal one, since the volume of the muscles into which the injected fluid passes is large, and the record is taken from more than one muscle.

What we have termed the tibial group consists of the tibialis anterior and the two dorsiflexors of the toes, which are bound together in very intimate relation, especially near their origins from the tibia. The skin was incised and the grouped tendons were tied together at the point of insertion of the tibialis anterior. The muscle group was then freed down to its origin at the head of the tibia, the few vessels running from the muscle belly to the tibial artery being tied. This vessel was now ligated at a point about half-way along the tibia, where it is beginning to emerge from the interosseous membrane, and freed as high as possible, all branches being tied. The vessels actually supplying the tibial group are usually so inaccessible as to be well protected from accidental ligature. The popliteal space was now opened by an incision along the outer side of the femur, care being taken to avoid the peroneal nerve, which should lie just posterior to the line of the incision. The popliteal artery was defined, and drawn into a more accessible position by a loose thread around it, and the posterior tibial artery was tied, together with two small muscular branches. This leaves open the anterior tibial vessel which eventually supplies the tibial group. The thread was left round the popliteal artery, and the wound in the thigh was loosely closed. A clamp was now applied to the tibial artery a short distance above the point at which it was tied, and a needle cannula was inserted centrally into the tibial artery just proximal to the point at which it was tied. Arterial injections were made by attaching a charged syringe to this cannula, closing the popliteal artery by traction on the thread around it, opening the clamp on the tibial artery, and briskly emptying the syringe into the arterial system of the muscle. All solutions were injected in a volume of 2 c.c.

For the myographic recording of the tibial group, of the gastrocnemius and of the soleus, the lower limb was immobilized by inserting drills in the lower and upper ends of the tibia and the upper end of the femur, and clamping them rigidly to uprights bolted to the T slots of a large machined bed-plate. The bed-plate carried at one end a hollow bronze pillar, 7·6 cm. in diameter, on which were mounted on movable bosses one bronze tube to carry the drill in the lower end of the tibia and another reinforced bronze tube to carry the myograph proper. The myograph was a flat steel cantilever, the flexions of which under tension were recorded by a mirror. The connexion between tendon and myograph was through a stout steel hook interrupted by an insulating section of fibre.

In some experiments we used the inferior oblique muscle of the eye for electrical, but not for mechanical recording. The lower eyelid was removed and the bone of the lower margin of the orbit, to the extent of about 1 cm., was excised. The conjunctival sac was then opened at the lower pole of the globe and the orbital tissues dissected, until the tendon of the muscle could be located and tied. The globe was then punctured, freed from any attachment to the inferior oblique muscle, and removed. Careful dissection from the middle of the muscle towards the depths of the orbit exposed the branch of the 3rd cranial nerve supplying the muscle. This was freed at its junction with the ciliary ganglion, tied and cut. With reasonable care, there is no danger of interfering with the blood supply of the muscle. Beyond securing the thread attached to the tendon and supporting the head with sand bags no elaborate fixation was necessary for our immediate purpose.

We have found it desirable to maintain constant the temperature and humidity of the air surrounding the muscles exposed for recording. For this purpose we used a transparent celluloid box, warmed by two 36 watt lamps, covered with wicks dipping into distilled water. The hook attached to the tendon passed through a small hole in the top of the box, and the bottom of the box carried a skirt of rubber-dam with which a reasonably air-tight joint could be made between the lower edge of the box and the thigh muscles, with the necessary stands and clamps. A similar smaller box was used for the eye muscle. With this arrangement, the temperature could be kept at any desired level up to 40° C. and complete saturation with water vapour maintained.

For excitation of the nerves supplying gastrocnemius, soleus or the tibial group, two pairs of electrodes in a common insulating cover were applied to the sciatic nerve in the thigh, in such a way that the nerve could be returned to its natural position, and the muscles and skin sutured over it. The two cathodes of the paired electrodes were 1·8 cm. apart, and were both placed peripherally to, and on the side of the nerve opposite to the anodes. In most experiments the first of a pair of single stimuli, and tetani in all cases, were applied through the centrally placed electrodes, and the second stimulus of a pair or both of the pair following a tetanus, through the peripheral electrodes. In the case of the inferior oblique muscle of the eye, the stimuli were applied through a single pair of electrodes placed on the nerve, 1 cm. away from the muscle.

The stimuli were taken from the secondaries of air-cored transformers actuated by the condenser discharges from gas discharge tube circuits (Schmitt, 1932). They were timed by a Lucas pendulum.

For electrical recording we led from belly-tendon by means of small silver pins, the belly lead being earthed and the tendon lead making connexion with the grid of the first stage of a two-valve condenser coupled amplifier, which fed the output stage either of a Matthews' or of a cathode ray oscillograph. The condensers and leaks were of such size that a rectangular pulse gave a deflexion falling to 1/2 value in 0·5 sec. For recording with concentric needle electrodes we used four stages, coupled with small condensers, feeding either a loud speaker or a Matthews' oscillograph output stage.

Acetylcholine chloride was freshly prepared in saline, acidified to pH 4, and eserine and atropine sulphate and quinine hydrochloride solutions were similarly prepared. Purified curarine chloride (King, 1935) was used for producing neuromuscular block. It was only used by local arterial injection in doses which, although fully effective in the muscle under investigation, were without any detectable general effects.

In the investigation of the effects of denervation, we divided the sciatic nerve, under full anæsthesia and with aseptic precautions, through a small incision in the lateral side of the thigh.

RESULTS.

General Behaviour of the Myotonic Animal.

Full descriptions of the behaviour of these myotonic goats have already been published (*see* Kolb, 1938), and we have little to add to them. The animals may appear perfectly normal when feeding quietly, but sudden exertion of any kind produces the myotonic seizure. The muscles of the flexors and extensors of the limbs are rigidly contracted and stand out beneath the skin. The limbs are immobilized in extension and the animal may fall. After a few seconds the rigidity passes off, and, after one or two failures, the animal regains its feet and can walk away with little disability beyond a stiffness in the limbs. The effects of rest and of different types of exertion are very striking. A myotonic goat, seen for the first time late in the day, after it has been indulging in continuous mild exercise, appears practically normal. If it is now thrown, and made to lie still for three to five minutes, extreme myotonia develops as soon as it has made the convulsive effort of rising to its feet. Similarly, the stiffness of the legs is always worse when the animals are visited early in the morning.

The effect of sudden exertion is most strikingly shown when the animals attempt to jump. The loose box in which our goats were kept contained a low food trough. Two goats, which showed relatively little myotonia with ordinary tests, regularly attempted to jump into this when approached. They were able to insert their fore-limbs, but the effort of jumping produced a myotonic contraction of the hind-limbs of such severity that they remained immobilized for some minutes.

The pronounced influence of rest and of various types of exertion on the degree of myotonia led us to adopt a method of testing, designed to make the conditions as much under control as possible. The goats were suspended in a metal frame from a horizontal bar, 1·5 m. above the ground, by means of two strips of webbing 20 cm. wide, one passing under the chest immediately posterior to the fore-limbs and the other under the belly just anterior to the hind-limbs. The ends of the strips were attached to the horizontal bar by catches, which could be released suddenly and simultaneously. The goats were lifted into position with as little disturbance as possible, and suspended with their feet just clear of the ground for a given time. During the period of suspension they usually rested quietly without any struggling or attempts to free themselves. When the catches were released, the goats invariably ran forward one or two steps before they were immobilized by the myotonia. The time between dropping and the moment of crossing a low step leading to their dwelling was taken as an index of the degree of myotonia.

Tested in this way, four of the goats have shown remarkable constancy in their responses over a period of months. Thus, after three minutes suspension, the time in one animal has varied between ten and fifteen seconds, and in a third seven and twelve seconds. An increase in the time of suspension increases the duration of the myotonic rigidity ; one animal, which had given figures of eight and six seconds in the two previous tests with three minutes suspension, took fourteen seconds to pass the step after a suspension of five minutes. A fifth goat showed much less myotonia and more variation in the degree. On one occasion she showed no stiffness after three and ten minutes suspension and only six seconds after fifteen minutes. On another day she showed fifteen seconds of stiffness after a rest of only five minutes.

It is perhaps worthy of notice that the change in environment and diet, consequent on the removal of the goats from a Tennessee farm to the Medical Research Council's farm at Mill Hill, does not appear seriously to have altered the myotonia. One of the animals now in our possession was the subject of some studies by Dr. Kolb in 1938, and he informs us that, although it is difficult to make accurate comparisons, there seems to be little alteration in the degree of her myotonia.

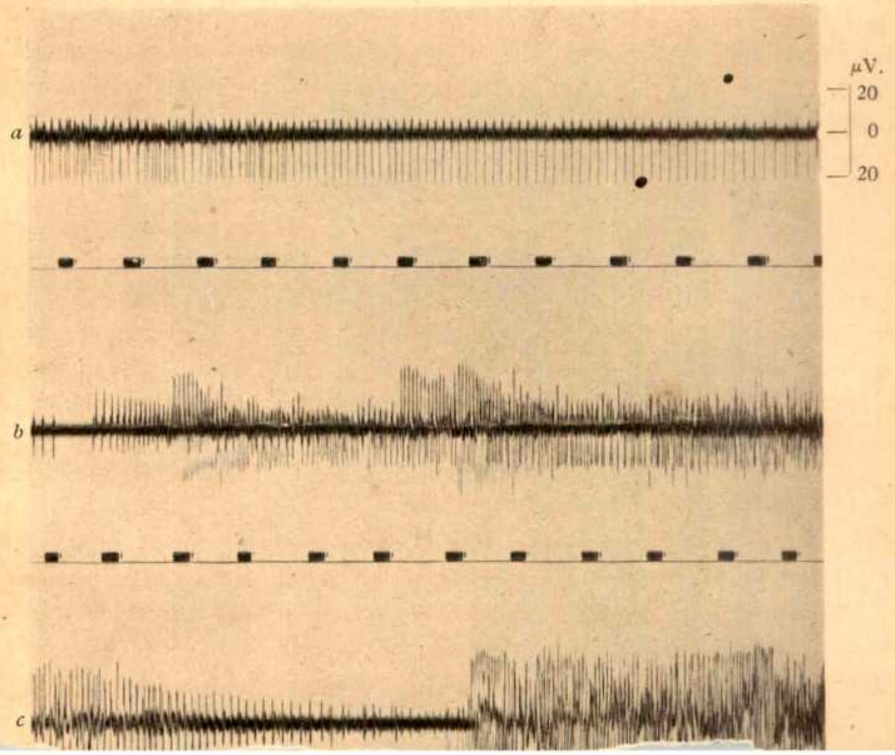
These animals show very clearly the local response of the muscle to mechanical stimulation, which is so characteristic of myotonia in man. We clipped the hair over the region of the hamstring muscles, and, with the leg flexed on the belly, struck the skin over the muscle sharply with a percussion hammer. The resisting contraction raised the skin into a roughly spherical swelling some 7 cm. in diameter and 2 cm. in height, which persisted for five to ten seconds. Such a response can be elicited regularly and can be repeated indefinitely, provided a few seconds are allowed to elapse between each blow. We have observed an analogous response also in the fore-limb, tongue and trunk muscles, but it is most easy to elicit in the hind-limb. The contraction resulting from striking is sufficiently strong to cause movements of a limb. If the animal is supine and the hind-limb is flexed at the hip, with the knee and hock at the same level, a blow on the tibialis group of muscles causes a brisk elevation of the foot, which stays raised for some five seconds, and then gradually falls back to its previous position.

These local responses to mechanical stimulation are not obviously diminished by full surgical anæsthesia.

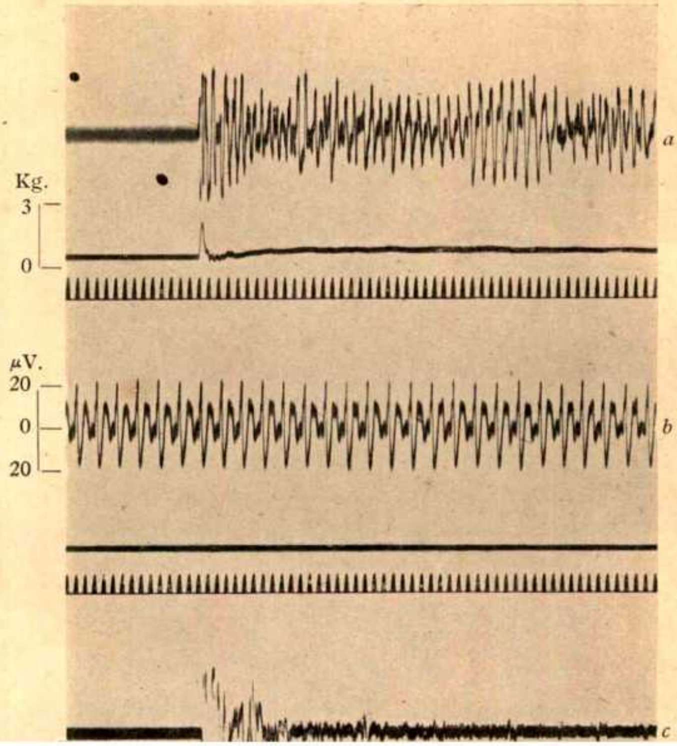
Examination with Needle Electrodes.

The goats were anæsthetized with nembutal and the electrical behaviour of the muscles was examined by inserting concentric needle electrodes.

The immediate effect of inserting an electrode into one of these muscles is very striking, and more particularly so if the amplified action potentials are led into a loud-speaker. The muscle appears to be in a state of incessant activity. Groups of fibres suddenly commence to fire at frequencies



there appears to be little, if any, entirely spontaneous activity. The muscle, however, is exquisitely sensitive to mechanical stimuli ; even stroking the skin with the finger over or near the recording electrode is sufficient to set up intense activity (fig. 1). As might be expected, tapping or stretching



of the needle show potentials so constant in size and frequency, and of such magnitude, as to suggest that they are the responses of single muscle fibres. In other cases, the size and constancy of the discharges suggest that the response is due to the synchronized discharge of single motor units. Fig. 2*b* shows a particularly striking example of such a response of constant frequency which is too great to be due to a single fibre and is almost certainly due to the synchronized potential changes in the fibres of at least a motor unit.

We have tested thus with concentric needle electrodes the flexors and extensors of both fore- and hind-limbs, and also the extrinsic ocular muscles and from all of these the abnormal discharges have been recorded.

The response of the muscle of a normal anæsthetized goat to tapping is strikingly different from the myotonic response. The blow is followed by a brief outburst of very asynchronous potentials, which lasts at the most one second (fig. 2*c*).

Effect of Nerve Section.

Isolation of the myotonic muscles from the central nervous system by section of their nerves produces no obvious alteration in their responsiveness to mechanical stimulation. In one animal, we divided the sciatic nerve aseptically in the thigh, and examined the leg muscles with concentric needle electrodes on alternate days for eight days. We could detect no diminution whatsoever in the responsiveness of the muscle to mechanical stimulation; in fact, we received the impression that any change was in the direction of an increase.

It should be noted that in the normal animal, also, decentralization of a muscle or degeneration of its nerve does not diminish the brief discharge which is evoked by tapping.

Myographic Examination.

(*a*) *Response to Single Nerve Volleys.*—The isometric tension maximum attained by the myotonic muscle, in response to a single maximal shock applied to its nerve, is greatly in excess of that of the corresponding muscle of a normal English goat of similar weight. For instance, the twitch-tensions recorded in the tibialis muscles of normal goats, between 16 kg. and 25 kg. body-weight, were from 1·1 kg. to 2·6 kg., whereas the tensions recorded in the myotonic goats were between 3·7 kg. and 4·4 kg. The duration of the twitch, if it is measured from the beginning of tension development to half-relaxation in warm muscles, shows only a slight difference between normal and myotonic muscles, but the time to full relaxation is longer in the myotonic. Thus, single maximal twitches of normal tibialis muscles had a duration to half relaxation of 120 msec., and to full relaxation of 170 msec.; myotonic tibialis muscles gave figures of 150 msec. and 260 msec. for the same intervals.

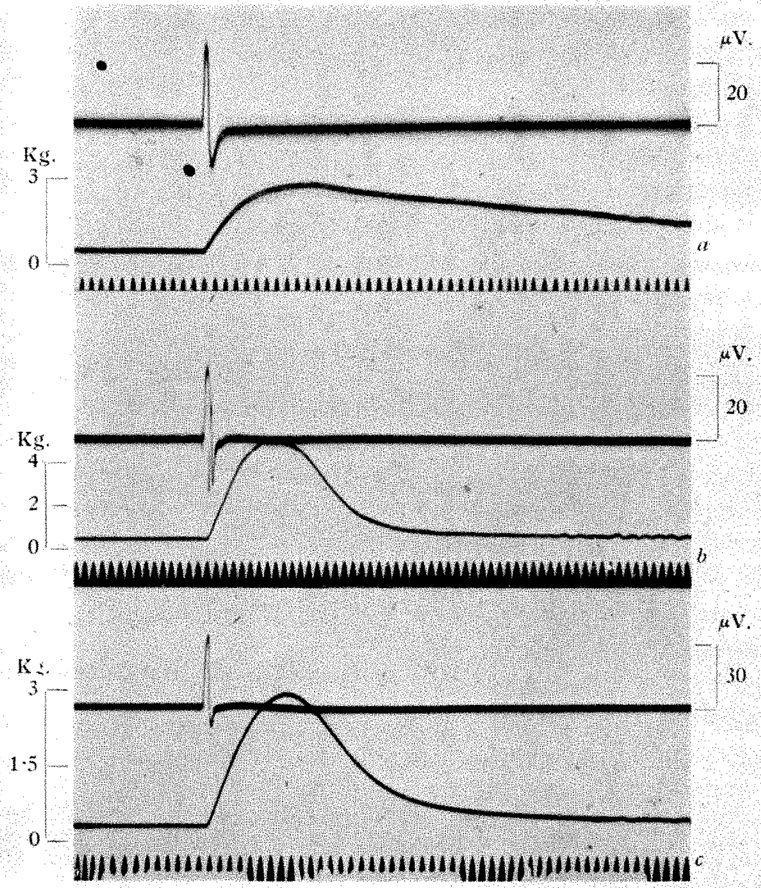


FIG. 3.—Myogram and action potential (belly-tendon) in response to single maximal nerve volley. (*a*) Normal tibial group (muscle cold); (*b*) myotonic tibial group; (*c*) myotonic soleus, another goat. Time 10 msec.

The Action Potential.—The action potential, recorded from belly to tendon, may show relatively little abnormality, or it may be clearly repetitive (fig. 3). Fig. 3*b* was taken from the tibialis group of a goat which showed less myotonia in both physical and myographic examination than the goat from which fig. 3*c* was obtained. The peculiarities of the myotonic muscle are best revealed by the use of the more localized lead provided by concentric needle electrodes. Fig. 4 shows the prolonged discharge which may follow a single nerve volley. The use of concentric needles also brings out very strikingly the effects of repeated stimulation; the first of a series of responses always shows much more repetitiveness than the last, and, incidentally, the twitch-tension is greater in the earlier responses of a series. Such a decline in twitch-tension during a series is abnormal, since normal muscles always show some degree of "staircase effect."

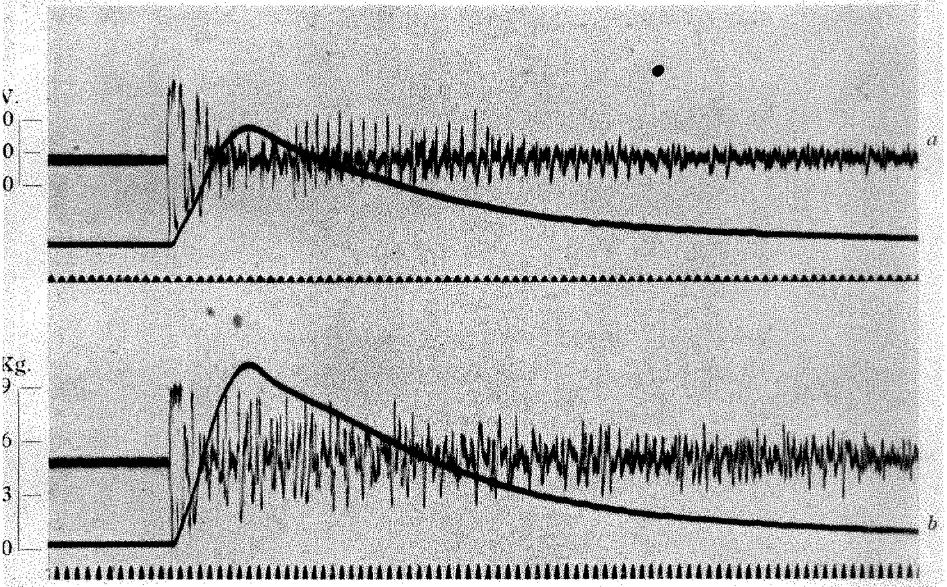


FIG. 4.—Myogram and action potential (concentric needle) of myotonic tibial group in response to (*a*) single maximal nerve volley; (*b*) two volleys 7 msec. apart.

(*b*) *Response to Double Nerve Volleys.*—We have made some determinations of the least interval at which two nerve volleys produce two responses in the muscle. The most accurate measurements have been made on the electrical responses of the 3rd nerve—inferior oblique muscle preparation, which, as we pointed out above, shows myotonia to a degree little different from the other muscles. In the normal goat, a second electrical response in the muscle appears when the stimuli are applied to the nerve 0·7 to 0·8 msec. apart and the second electrical response is equal to the first when they are 3 msec. apart. In the myotonic goat a second response appears at the same intervals, and the recovery curve of the second action potential does not differ significantly from the normal. Similar determinations on the soleus muscle and the tibialis group show that in both normal and myotonic muscles of the hind-limb a second response is just detectable when the second stimulus to the nerve follows the first after 1 to 1·5 msec. The muscular summation curve, relating tension maximum to intervals between two nerve volleys, does not differ significantly in the normal and the myotonic muscles.

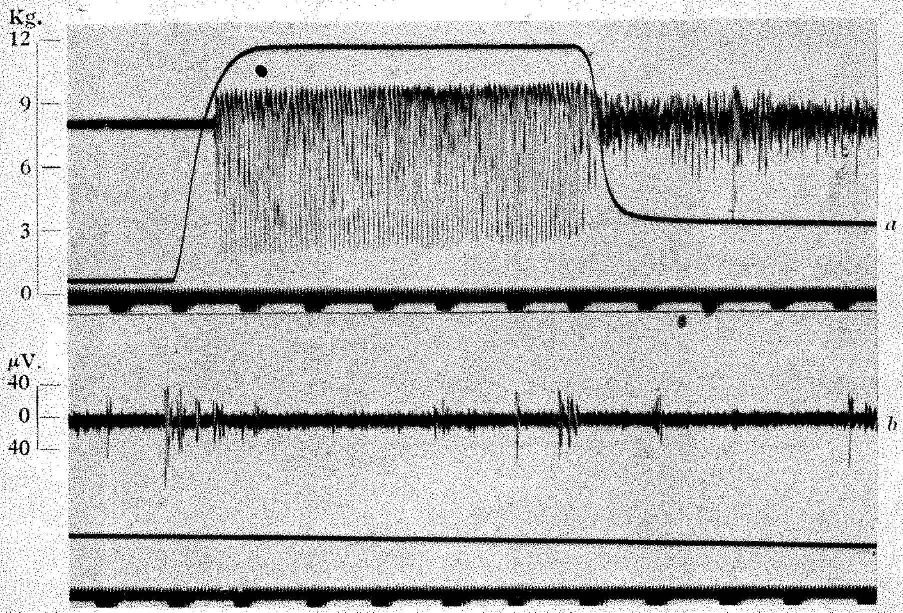


FIG. 5.—Myogram and action potential (concentric needle) of myotonic tibial group. (*a*) Response to maximal stimulation of nerve at 50 per sec.; (*b*) 10 sec. later. Time 10 and 200 msec.

The amount of repetitive discharge in the myotonic muscles is much greater after two nerve volleys than after one, if the interval separating the volleys is less than 10 msec. It is, of course, very difficult to make any quantitative comparison, on account of uncontrolled movements of the needle electrodes and variations due to the amount of previous stimulation but, as shown in fig. 4, the intensity and duration of the repetition after two nerve volleys are much greater than after a single volley.

Effects of Tetanic Stimulation of the Nerve.

The ratio between the single twitch tension and that developed in a fully fused, maximal tetanus is little different in the myotonic goat from the ratio observed in the normal animal. Figures of 2·5 to 3 are usual in the tibialis group of both types.

The most striking result of a tetanic stimulation of the nerve of a myotonic muscle at frequencies at, or about, the fusion frequency, i.e. 60 to 80 per second, is the prolonged maintenance of tension by the muscle after the stimulation has been interrupted. As shown in fig. 5, a stimulation at 50 per second for 1·2 seconds may be followed by a persisting contraction of quite considerable tension. In this particular experiment, the muscle had not completely relaxed to its initial tension some 15 seconds after the end of the stimulation. As is clear from the illustration, this after-contraction is accompanied by oscillatory action potentials in the muscle. The resemblance between this long persisting contraction and the rigidity following a sudden voluntary effort is sufficiently obvious to need no further comment.

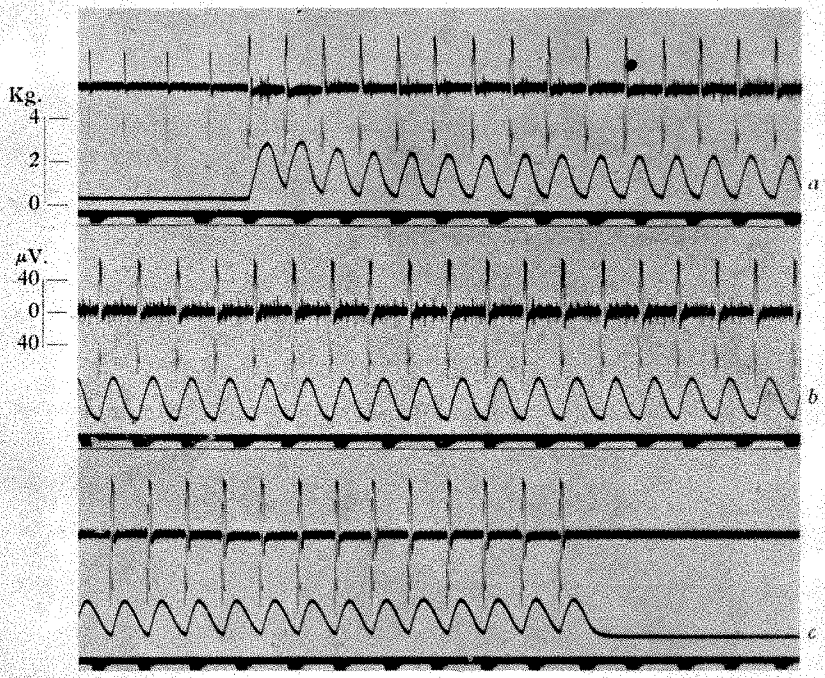


FIG. 6.—Myogram and action potential (concentric needle) of myotonic tibial group. (*a* and *b*) Continuous record of response to nerve stimulation at 7 per sec.; (*c*) 10 sec. after. Time 0·2 sec.

The effects of stimulation of the motor nerve at frequencies well below the tetanic fusion frequency are strikingly different from the effects of higher frequency stimulation. There is usually a slight increase in the degree of repetitive discharge during the first few responses, but, as the excitation is continued, the repetitiveness diminishes, and, at the end of the stimulation, the response may be little different from that of a normal muscle (fig. 6). Again, it is hardly necessary to point out the similarity between this phenomenon and the relief of the myotonic symptoms by the rhythmic activity of mild exercise.

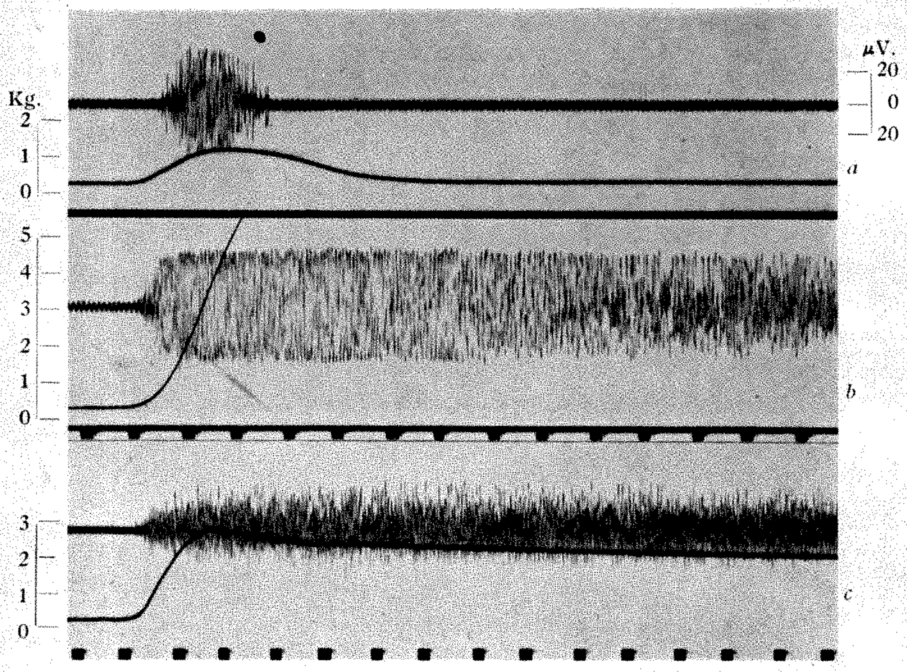


FIG. 7.—Myogram and action potential (concentric needle) of tibial group in response to arterial injections of acetylcholine. (*a*) Normal goat, 100 μg.; (*b*) myotonic goat, 100 μg.; (*c*) myotonic goat, denervated muscle, 2 μg. Time 0·2 sec.

Reactions to Acetylcholine.

As we have already pointed out, the goat does not offer any particularly suitable preparation for the technique of close-arterial injection. The tibialis group is in many respects the most satisfactory, and in normal goats responses equal in tension to the maximal nerve twitch-tension have been obtained with doses of acetylcholine of between 20 and 100 μg., injected into the blood-vessels of the muscles in a volume of 2 c.c. These responses are, as in the cat, brief and twitch-like, and are accompanied by a brief outburst of oscillatory action potentials (fig. 7).

In the myotonic muscle, the dose required to produce a contraction equal in maximum tension to the twitch-tension has varied between 50 μg. and 100 μg. Although approximately the same doses of acetylcholine are required to produce an equivalent tension maximum in the myotonic as in the normal muscle, a given dose of acetylcholine produces in the myotonic a response of very much greater duration. For instance, a myotonic muscle, which had received a dose of acetylcholine sufficient to produce a contraction equal to the maximal twitch-tension, had not fully relaxed 30 seconds after the injection. In a normal muscle a response of similar tension is over in less than one second (fig. 7). This response of the myotonic muscle to acetylcholine is accompanied throughout its long duration by action potentials.

We have investigated the effect of the prolonged contraction resulting from the injection of acetylcholine upon the response of the muscle to simultaneous excitation through its nerve. In one experiment, we stimulated the nerve with single maximal shocks at a frequency of one per second and, without intermitting the stimulation, we injected 100 μg. of acetylcholine in 2 c.c. into the arterial system of the muscle. The contraction in response to the acetylcholine was at least three times the twitch-tension, and lasted some 20 seconds. Measurements of the tension of twitches excited through the nerve during the acetylcholine response, and of their accompanying action potentials, showed that, even when superimposed upon a contraction of magnitude equal to the normal twitch-tension, the nerve twitch still attained 71 per cent. of its original strength, and that the action potentials were never reduced by more than 20 per cent.

Reactions to KCl.

Normal goat muscle is not particularly easy to excite by injected KCl. In one animal, a dose of 100 mg., injected arterially into the tibialis group in a volume of 2 c.c., produced a contraction, with a tension maximum only one-third that of the twitch-tension, and in another, a large goat of 72 kg. body-weight, 200 mg. produced only a just visible contraction. No dose of less than 40 mg. has evoked a perceptible response in this muscle group in any of our normal goats.

In the myotonic goat, on the other hand, 10 mg. in 2 c.c. produced a definite mechanical response, and 20 mg. caused a long lasting contraction, which reached a tension of 4·62 kg., or nearly double the nerve twitch-tension (fig. 8). In this particular instance, the contraction lasted more than three minutes, and throughout its course was accompanied by a violent, unbroken oscillatory electrical discharge (fig. 8). So sensitive, indeed, is the myotonic muscle to KCl that we have observed electrical outbursts resulting from injections of 4 mg. in 2 c.c., or only five times the normal concentration of KCl in Locke's solution. These responses seemed clearly to be the consequence of the raised K^+ concentration, since similar injections of isotonic NaCl solution were without effect.

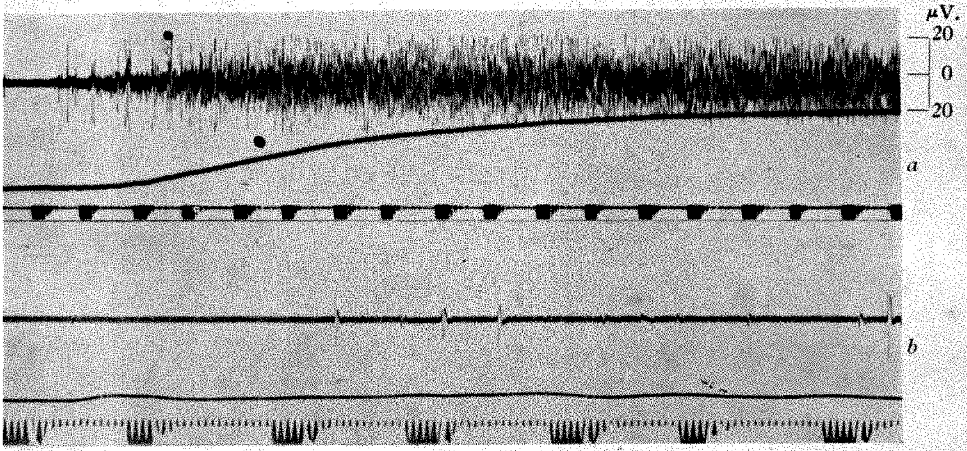


FIG. 8.—Myogram and action potential (concentric needle) of tibial group in response to arterial injection of KCl. (*a*) Myotonic goat, 20 mg.; (*b*) normal goat, 100 mg. Time 10 and 200 msec.

Effects of Curarine.

In the expectation that curarine would modify profoundly the myotonic phenomenon, we gave the drug by close-arterial injection in small, increasing doses. We found, however, that curarization of the muscle did not, at any stage, modify the characteristic responses of the myotonic muscle to mechanical stimulation. Thus, in one experiment, a dose of curarine, which had reduced the nerve twitch-tension to one-tenth of its original value, in no way altered the response of the muscle to tapping; and this latter response persisted unchanged when the muscle would no longer respond to nerve stimulation.

As might be expected from previous work (Brown, 1937*b*), full curarization is similarly without effect on the response of these muscles to KCl.

We have as yet insufficient data to justify any full account of the effects of curarine on the responses to injected acetylcholine. In normal muscle, acetylcholine ceases to be effective at a stage of curarization at which the motor-nerve twitch-tension is not yet greatly reduced. In the one experiment which we have made on the myotonic goat, the response to 100 μg. acetylcholine was reduced to one-seventh of its previous value by a dose of curarine which had just eliminated a visible tension response to nerve stimulation.

Effects of Denervation.

As we have stated above, division and degeneration of the nerve supply of the myotonic muscle has no immediate effect upon its abnormal sensitivity to mechanical stimulation.

Denervation, as in normal muscle, increases the sensitivity of myotonic muscle to injected acetylcholine. An injection of 2 μg. of acetylcholine produced a contraction attaining a maximum tension of 2·2 kg., which was of such duration that it had not quite attained one-half relaxation in 20 seconds (fig. 7). An injection of 10 μg. produced a response of 4·3 kg. and of similar duration. Both these responses were accompanied throughout their course by oscillatory action potentials, and, in fact, we have not observed, with doses of acetylcholine up to 10 μg., any sign of the characteristic "silent period" which accompanies the responses to acetylcholine of large tension in the denervated muscle of a normal animal. Denervated myotonic muscle responds readily to KCl injections, and probably shows some degree of sensitization as compared with the innervated myotonic muscle. A very prolonged response, accompanied throughout by oscillatory potentials, and attaining 2·1 kg. tension was obtained with 10 mg. of KCl, injected arterially into the tibial group of a myotonic goat.

Effect of Other Alkaloids.

The known curative effect of quinine on myotonia, both in man (Wolf, 1936) and in the goat (Kolb, 1938), led us to examine the effects of this substance on the abnormal sensitivity to mechanical stimulation. Fig. 9 illustrates its actions, and is of additional interest in that the responses were recorded from a muscle which had been denervated for eight days, and had already received a full dose of curarine. In A is shown the effect of a tap applied to the belly of the muscle. Between A and B the muscle received 3·5 mg. of quinine by arterial injection. In B the muscle was again tapped, and gave a response little greater than that occurring in normal muscle.

Eserine, in a dose of 200 μg., injected arterially into the tibialis group of a normal goat, produces at least a 50 per cent. potentiation of the nerve twitch-tension. Into the corresponding muscle group of a myotonic goat we injected doses of 20 to 40 μg. of eserine without producing a recognizable modification of the nerve twitch. In a subsequent experiment, the injection of 200 μg. into the tibialis group of a myotonic goat produced a potentiation of twitch-tension little different in extent and duration from that observed in the normal animal. On this evidence we can only conclude that the myotonic muscle is not greatly, if at all, more sensitive to the action of eserine than is the normal muscle.

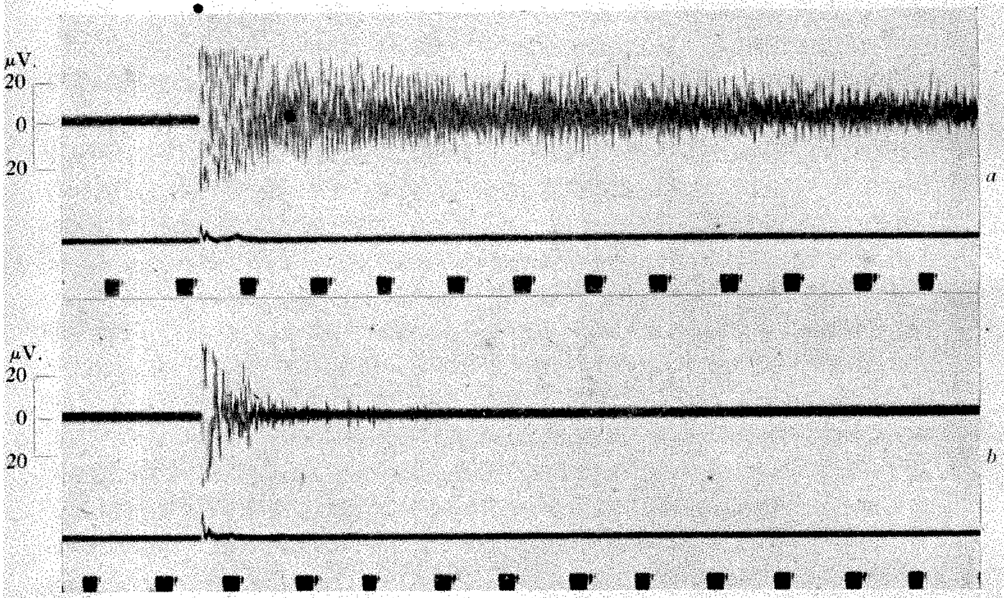


FIG. 9.—Myogram and action potential (concentric needle) of denervated and curarized myotonic tibial group in response to tapping. (*a*) Before and (*b*) after arterial injection of 3·5 mg. quinine. Time 0·2 sec.

DISCUSSION.

Most authors who have investigated goats suffering from this congenital abnormality have been in little doubt that the condition is so like Thomsen's disease in man as to be indistinguishable from it. With this view we fully concur. Apart from the stiffness which accompanies any sudden muscular activity, one of the most striking abnormalities to be seen, both in man and in the goat, is the local contraction of the muscles which results from a sharp blow upon them. It has been customary to refer to this as a "contracture," but our results make it quite clear that this description is incorrectly applied. A contracture in a muscle is an unpropagated, localized response, and, as such, has no accompanying action potential of the rapid type normally associated with propagated contraction.

Slow potential changes between the active and passive portions of a muscle in contraction may admittedly exist; but the true, rapid oscillatory wave accompanying a propagated contraction is characteristically absent (*cf.* Gasser, 1930; Brown, 1937 *a*). We have shown, we think beyond question, that every response of the myotonic muscle, whether to nerve stimulation, to mechanical stimulation, or to an injected chemical excitant, is accompanied by oscillatory action potentials. These responses must therefore be regarded as asynchronous, tetanic contractions of the muscle fibres, and not as contractures. The existence of these oscillatory potentials, as usually recorded by concentric needle electrodes, shows that some part at least of the muscle is in tetanic contraction, though it does not entirely exclude the possibility that a contracture may be involving some of the constituent fibres of the muscle other than those in immediate proximity to the electrodes. Another test, however, may be applied. The state of contracture in a muscle fibre prevents the propagation along it of excitation waves arising from the region of the motor end-plate (Brown, 1937 *a*). There is accordingly a great depression in the responsiveness of a muscle in contracture to stimuli applied to its nerve. We have shown, indeed, that there is some reduction, both in tension and in the action potential of the twitches superimposed on the prolonged response of a myotonic muscle to acetylcholine. This reduction, however, is certainly not too great to be explained by the fact that at any one moment many of the fibres are refractory, as a result of their continued tetanic response to acetylcholine. We are convinced, therefore, that the long-lasting developments of tension in myotonic muscles are due to normally propagated excitations in the fibres, and not to anything of the nature of unpropagated contracture.

Our experiments have given, we believe, an equally conclusive answer to the question of the involvement of the central nervous system in the pathogenesis of the disease. The characteristic responses to mechanical stimulation occur, without perceptible change, in the myotonic muscle, not only after full curarization, but after the nerve endings have degenerated as a result of section of the nerve to the muscle. It would obviously be difficult entirely to exclude the possibility that some abnormality of central discharge might be present, in addition to the demonstrable abnormality of the responding muscle; the symptoms of the disease, however, can be entirely explained by the observed abnormalities of the muscle. As we have pointed out, one of the most striking features of the disease is due to the fact that the symptoms are intensified, or, indeed, may only become apparent, after a sudden muscular exertion. This might be thought to point to a central origin of the disease; but an after-contraction of long duration follows artificial tetanic stimulation of the cut nerve at suitable frequencies, and it is probable that a sudden sufficiently intense motoneurone discharge would have the same effect, given the same muscular abnormality. Such a motoneurone discharge of the range of frequency found to be most suitable for producing the after-contraction is, in fact, the normal cause of any sudden, vigorous muscular movement. The intensification of the myotonic state by tetanic stimulation or by sudden voluntary exertion, is readily explicable in terms of phenomena observed in the mammalian nerve-muscle preparations. Tetanic stimulation of the motor nerve of a muscle produces an increase in the tension of subsequent twitches, and a long-lasting increase in the excitability of the motor end plates. It has been shown that both these after-effects of a tetanus are probably due to K ions mobilized by the intense activity of the muscle (Brown and Euler, 1938). We have shown that the myotonic muscle is abnormally sensitive to K^+ and this would render it more susceptible than the normal to the after-effects of tetanization.

The effects of mild continuous exercise and, experimentally, of tetanic stimulation at frequencies well below the fusion rate, in relieving the myotonia, are again compatible with known properties of mammalian muscle. Low frequency stimulation, unlike high frequency, can be shown to depress still further the responses of a preparation in which neuromuscular transmission has been partially blocked by curarine (Brown, 1938).

It appears, then, that the myotonia is due to an abnormality of some part of the muscle fibre itself, since the abnormal response of the muscle to direct excitation is essentially unaltered by severance of the nerve, by blocking neuro-muscular transmission with curarine, and even by degeneration of the motor nerve endings. The essential abnormality appears to be a tendency of the muscle fibres to respond repetitively to any form of stimulation. There are certain features of this repetitive discharge which make it remarkable. There is little synchronization among the fibres of the muscle as a whole, judging from the electrical records taken with belly-tendon leads. Examination of fig. 3 shows that, even with this lead, there may be a second distinct spike after the first synchronous response to a single nerve volley, but, as often as not, the repetitiveness is shown by little more than an irregularity in the descending limb and diphasic artefact of the response. The synchronization is, in fact, very much less than is observed in the repetitive discharge which follows single nerve volleys in normal muscle after the administration of eserine in suitable doses (*cf.* Brown, Dale and Feldberg, 1936). The frequency of the discharge, then, would seem to vary from group to group of muscle fibres, after a single stimulus has been applied. There seems, however, to be some mechanism which gives rise to a local synchronization, since the regular and very long lasting discharges which follow insertion of needles, or, in some cases, tapping the muscle, seem too large to be confined to single muscle fibres, and suggest that the fibres of a motor unit are contracting in very perfect unison. We are unable at present to commit ourselves to any explanation of this synchronization.

In many respects, there is a very close similarity between a muscle in myotonia and one poisoned with veratrine (*cf.* Eichler, 1938; Kolb, Harvey and Whitehill, 1938). Both show prolonged and very asynchronous repetitive responses to single nerve volleys, and in both the abnormalities persist after denervation and full curarization (Bacq and Brown, 1937). Some preliminary experiments which we have made show that a veratrinized muscle exhibits a sensitivity to mechanical stimulation very like that of the myotonic muscle. There is one further point in which the effects of veratrine are particularly suggestive. Bacq (1939) has recently shown that veratrine has a very remarkable effect on frogs' muscle, in sensitizing it to the effects of K ions, and the myotonic muscle is notably sensitive to the same ions. K ions alone, in quite low concentrations, can stimulate many excitable structures, and in sub-liminal concentrations increase the excitability of tissues to other stimuli. Excitation of a muscle certainly causes a mobilization of K ions and even actual loss of K^+, and there is reason to suppose that the myotonic muscle may lose K^+ in excess (Cumings, 1939).

Some mention may be made here of the therapeutic effects of various substances in man and their actions in the goats. Myotonia in both man and goat is relieved by quinine and certain quinine derivatives (*cf.* Kolb, 1938), and we have shown here that the typical response to tapping is absent after the administration of quinine. In the course of a study of the actions of quinine, Harvey (1939, *a* and *b*) found that two of many were likely to be responsible for its curative effects in myotonia, one being its curare-like effect and the other its ability to suppress repetitive responses of all types. Our present work shows that it is probably the latter which is mainly responsible. Any curarizing substance would probably relieve the myotonic symptoms in some degree, simply by diminishing the amount of excitation reaching the muscle; but, as we have shown, no amount of curarine will abolish the abnormal response of the muscle to mechanical stimulation.

Eserine and its analogues, which have such dramatic effects on normal muscle, might be expected to accentuate the symptoms of myotonia, as clinical experience in man has shown them to do (Russell and Stedman, 1936). This action, however, should not be taken as indicative that an abnormality of the neuromuscular transmitting apparatus necessarily contributes to the peculiar behaviour of the myotonic muscle. In normal muscle eserine changes the response to a single nerve volley from a single contraction into a brief tetanus, and there is no reason to suppose, therefore, that it should do other than accentuate the existing repetitiveness of the response of the myotonic muscle. In any case, an action of eserine in any particular condition should be interpreted with caution since, in addition to its specific effect in protecting choline esters from enzymatic hydrolysis, it can change the direct electrical excitability of the muscle fibre.

SUMMARY.

(1) We have examined myographically and electrically the muscles of goats suffering from a congenital myotonia indistinguishable from Thomsen's disease in man.

(2) The muscles are extremely sensitive to mechanical stimulation; tapping, stretching and the insertion of electrodes cause contraction of the muscle.

(3) This contraction is due to a long-lasting irregular tetanus in groups of muscle fibres, best shown by means of concentric needle electrodes. It persists unchanged after section and degeneration of the nerve and after full curarization of the muscle, but is abolished by a suitable dose of quinine.

(4) The response of the muscle to a single nerve volley is repetitive, and the twitch-tension is greater than in a normal goat.

(5) Tetanic stimulation of the motor nerve at frequencies of the order of fifty per second aggravates the myotonia, and the muscle remains tetanically contracted after the stimulation has stopped. Stimulation at five per second, on the other hand, produces a progressive diminution of the abnormal activity.

(6) The myotonic muscles are not abnormally sensitive to acetylcholine, in that the amount required to produce a given tension maximum is approximately the same as in normal muscle. The duration of the response to a given dose is, however, greatly prolonged in the myotonic.

(7) The myotonic muscles are abnormally sensitive to potassium ions. A dose of KCl which has no effect in normal muscle produces a contraction of considerable tension, lasting some minutes in the myotonic muscle.

(8) Myotonia appears to be due to an abnormality of the muscle fibre

itself, and the neuromuscular transmitting apparatus is not directly involved.

We wish to express our gratitude to the Rockefeller Foundation and to Mr. J. J. Murray. Dr. James Ward, Professor Sam Clark and Dr. O. R. Langworthy for the assistance they gave us in obtaining and transporting the goats.

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BSERVATIONS ON THE EFFECTS OF TRIGEMINAL DENERVATION.

BY G. F. ROWBOTHAM

n the Neuro-surgical Clinic of the Manchester Royal Infirmary. This work arried out under a Research Fellowship in the Neuro-surgical Service of the Manchester Royal Infirmary.)

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I.—INTRODUCTION.

HE following study has been made in order to discover the iological effects of trigeminal denervation; it is not devoted to the ing of areas of resulting anæsthesia, nor is it concerned with the more peutic side of the results though it is interesting to note that in 95 per of the cases a complete relief from pain has been obtained.

ight hundred people have been treated in this clinic for primary minal neuralgia, root section has been performed on 291 occasions, here have been two deaths. In the whole series all kinds of operations been used: avulsion of the supra-orbital, infra-orbital and inferior l nerves; alcohol injection in the ganglion and into the second and divisions; intracranial neurectomy of divisions 2, 3 and 1 (in order equency); posterior root section in the middle and in the posterior and division of the trigeminal tract in the medulla oblongata. These riences have allowed observations on the changes following severance e trigeminal pathways and particularly on alterations in taste, on the vation of the cornea, on the proprioceptive pathways of the tongue, on ges relevant to the sympathetic nervous system, and on the ætiology of ytic keratitis.

MATERIAL.—FIFTY CASES OF TRIGEMINAL DENERVATION.

Root section by the lateral route :—	
Complete ...	8
Fractional ...	10
Root section by posterior fossa route	5
Intracranial neurectomy of division 2	4
Intracranial neurectomy of division 1	1
Alcohol injection :—	
Ganglion ...	10
Divisions ...	5
Tractotomy	5
Bilateral denervations ...	2
Total number of cases ...	50

II.—THE SENSE OF TASTE IN THE MOUTH.

In this section an analysis of the changes in taste which accompany trigeminal denervation of the mouth is made and an explanation given to account for their occurrence.

History.—Though the sense of taste has aroused the scientific curiosity of physicians since the days of Æsculapius, it was not until the beginning of the nineteenth century that sustained efforts were made to solve the problems of the anatomy of the gustatory pathways. That these problems have not been finally solved will not cause undue surprise. Any work on the sensory side of the nervous system is beset with particular difficulties since animal experimentation has obvious limitations and quantitative measurements in man are dependent on what must be variable factors, the personal evaluation of a stimulus and the ability to describe the sensation with precision.

Magendie (1822), on dividing the 5th nerve intracranially in dogs discovered that the sense of taste was lost on the anæsthetic side of the tongue. Coming from a scientist of Magendie's reputation this discovery was generally accepted, and obviously influenced the opinion of his successor Claude Bernard.

Bernard, though well aware of the change in taste which accompanies some types of facial paralysis in man, and despite his demonstration of the loss following intracranial division of the facial nerve in dogs, was convinced that taste was conveyed by the trigeminal nerve, and suggested that division of the facial nerve removed a motor phenomenon about the trigeminal nerve endings necessary for the development of an adequate sensory impulse.

However, an alternative theory had already been advanced by Montault (1833) in a thesis entitled " Dissertation sur l'hémiplégie faciale " in which loss of taste over the anterior two-thirds of the tongue was described in three cases of facial paralysis in man. The accuracy of this important finding has been sustained on many subsequent occasions, but at the time it added obscurity rather than clarity to the gustatory problems.

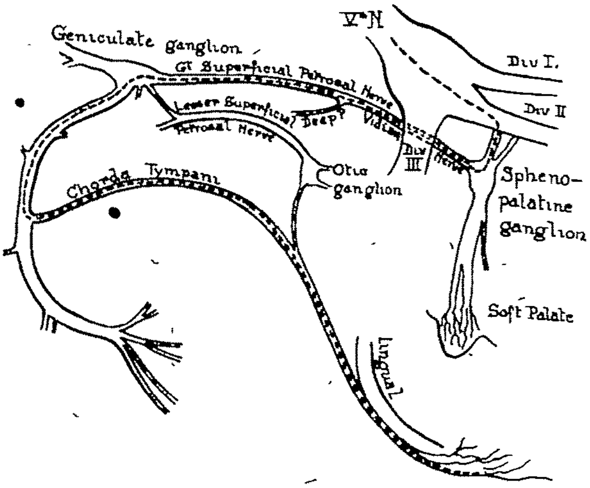

FIG. 1.—The pathway for taste fibres suggested by Schiff.

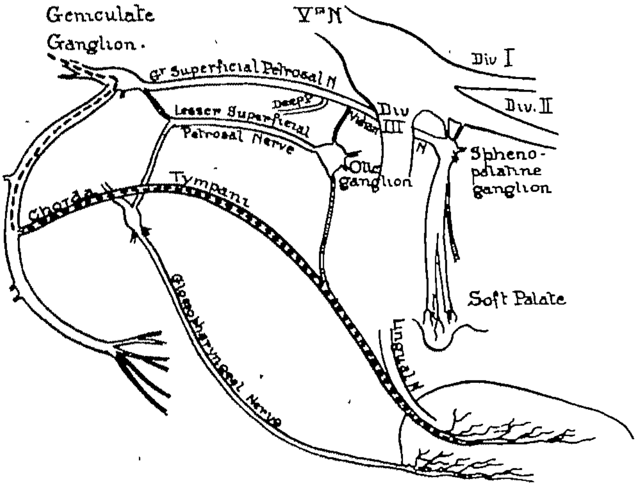

FIG. 2.—The pathway for taste fibres suggested by Lussana.

Thirty-four years later Schiff (fig. 1), as a result of his experiments on animals, believed that taste sensations were conveyed by the chorda tympani to the geniculate ganglion of the facial nerve, then along the great superficial petrosal nerve via Meckel's ganglion to the second division of the trigeminus and so by its posterior root to the brain.

On clinical evidence Lussana (1869) (fig. 2) came to the conclusion that the pathways were not so circuitous ; he expounded what has proved to be the modern belief that gustatory fibres are conveyed from the tongue by the chorda tympani nerve to the geniculate ganglion and then pass along the nervus pars intermedius Wrisbergii. This view was not generally accepted and Ziehl (1889) (fig. 3), as Schiff had done earlier, suggested that the trigeminus was the final pathway, the fibres entering the third division after passing through the geniculate and the otic ganglia. Gowers all his life was very strongly convinced that the 5th nerve was the main gustatory pathway from the mouth, and this opinion he declared quite firmly on several occasions. Very strong views were expressed by Dixon, an anatomist, against the trigeminal theory, and he argued on embryological grounds against it, pointing out that the nervus pars intermedius Wrisbergii is the post-ganglionic equivalent of the pre-ganglionic chorda tympani nerve, and so must relay gustatory impulses if the chorda tympani is a nerve of taste.

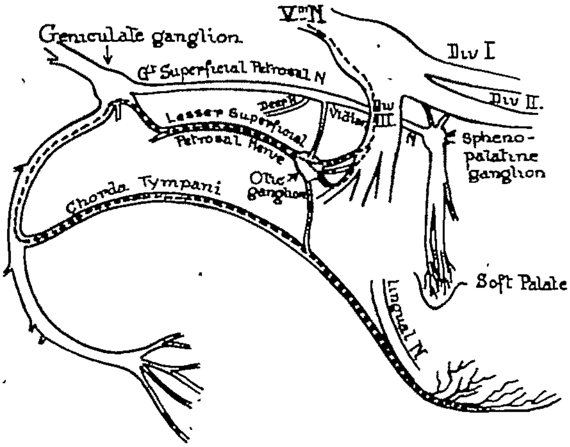

FIG. 3.—The pathway for taste fibres suggested by Ziehl.

New opportunities for study arose when Hartley (1892) and Krause (1892) succeeded in dividing the trigeminal pathways intracranially in man and again when the manœuvre was modified and perfected by Spiller and Frazier in 1909. Harvey Cushing (1903) reviewed thirteen cases of Gasserian ganglion extirpation and came to the conclusion that the trigeminus does not convey taste to the brain either from the posterior or anterior portion of the tongue. He did admit of a temporary abolition or lessening of acuity of the sense of taste over the anæsthetic part of the changes in the lingual nerve compressing or chemically blocking the fibr of the chorda tympani nerve. Dandy (1930), by the division of the 5th, 7t

TABLE I.—LIST OF CASES IN WHICH THE CONDITION OF TASTE WAS OBSERVED AFTE RESECTION OF THE GASSERIAN GANGLION.

(Compiled by Morriston Davies.)

Recorded by	Total	Taste unaffected	Taste impaired	Taste lost
Blüher	1	—	—	1
Cahen	1	—	—	1
Coelho	1	1	—	—
Dandridge	1	—	1	—
Depage	1	—	—	1
Erdmann	1	—	—	1
Eskridge and Rogers...	1	—	—	1
Garre	1	—	1	—
Hutchinson, J., Jun ...	1	—	—	1
Knock	1	—	1	—
Kruger	1	—	1	—
Marchant et Herbet ...	1	1	—	—
Monari	1	—	—	1
Stewart, R W. ...	1	—	—	1
Thomas, Lynn ...	1	1	—	—
Weeks	1	—	1	—
Winslow	1	—	—	1
Draudt	2	—	1	1
Friedrick	2	—	1	1
Rose	2	—	1	1
Thomas, H. M. ...	2	1	—	1
Keen	3	—	1	2
Maier	3	—	2	1
Pruschinin	4	—	3	1
Gowers	5	—	—	5
Lexer	6	—	—	6
Tiffany	6	4	—	2
Tiffany	10	4	6	—
Krause	6	1	3	2
Cushing	19	17	1	1
Davies	20	16	3	1
Total ...	107	46	27	34

and 9th peripheral nerves in the posterior fossa separately and in combin tion, made observations in man of great anatomical precision, and i collaboration with Dean Lewis reviewed his results (1930). They cam to the conclusion that section of the 5th nerve does not affect the sens of taste, and that taste sensations travel from the anterior two-thirds the tongue by the chorda tympani nerve and are relayed to the brain stem by the nerve of Wrisberg. The posterior third of the tongue is supplied by the glossopharyngeal nerve.

That the glossopharyngeal nerve and the nerve of Wrisberg are the main anatomical pathways of buccal taste there is little doubt, but there is still doubt about the importance of the trigeminal pathways. Wilfrid Harris (1926) was originally very certain that in most cases of trigeminal denervation the sense of taste is lost on the anæsthetic side of the tongue. He said " my clinical experience of 5th nerve paralysis due to disease and when produced by injection of the nerve at the foramen ovale, is, in my opinion, indubitable evidence of the gustatory function of the trigeminus." At first Harris inclined to the view that some taste fibres at least were conveyed by the trigeminal nerve, and in support of this thesis quoted Nageotte's histological research in which fibres leaving the trigeminal nucleus were demonstrated entering the neighbouring gustatory nucleus. As his experience widened he met with conflicting results, in some cases no gustatory changes being observed, and he reviewed his beliefs in less exclusive terms, suggesting that in some way or other there was a correlation and interdependence of function as regards taste in the facial, trigeminal and glossopharyngeal nerves.

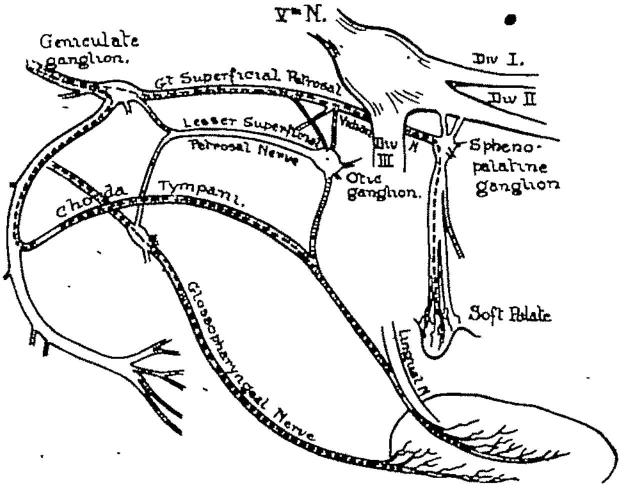

FIG. 4.—The modern conception of the pathways conveying the fibres of taste from the mouth. The finely dotted line denotes an alternative pathway by which the fibres of the chorda tympani nerve enter the geniculate ganglion via the great superficial petrosal nerve instead of coursing along the tympanic part of the facial nerve.

Carmichael and Woollard (1933) reviewed 17 cases of alcohol injection into the Gasserian ganglion made by Hinds Howell and they found that taste was lost in 10 of the cases.

Schwartz and Weddell (1938) (fig. 4) came to the conclusion that in some cases impulses subserving taste from the anterior two-thirds of the tongue pass along fibres which leave the chorda tympani to join the great superficial petrosal nerve before entering the geniculate ganglion. This alternative pathway has recently been confirmed by Wakeley and Mulvaney (1939). Damage to the great superficial petrosal nerve in this type of case will produce changes in buccal taste and it has been suggested that it is the variability of this pathway which accounts for the conflicting results found after trigeminal denervation.

This is the point at which the problem rests to-day.

Test 1.—With the tongue protruded a measured quantity of salt was placed on one side of the wet tongue 2 cm. backwards from the tip and 1 cm. medial from the border. With the tongue held gently between the examiner's fingers in the protruded position, the time in seconds was counted until the patient was able to signal his recognition of the taste by raising his hand and then making a statement or by pointing to a chart on which the name of the substance was written. The mouth was then washed until the traces of the salt had disappeared and a similar test carried out on the other side of the tongue. The tests were repeated with cane sugar, vinegar and powdered quinine sulphate.

Results.—Forty cases were tested by this method: twenty cases within fourteen days of the operation and twenty cases from two weeks up to five years after the operation. The average latent period before appreciation on the normally sensitive side of the tongue was thirty seconds.

Cases tested within fourteen days of the operation (usually on the second day):—

Taste was completely lost in	6 cases
Taste was delayed 30 seconds or more in	12 cases
Taste appreciated in the same time as on normal side in ...	2 cases

Cases tested fourteen days or more after the operation (usually several months later):—

Taste was completely lost in	2 cases
Taste was delayed 30 seconds or more in	14 cases
Taste appreciated in the same time as on normal side in ...	4 cases

Precautions were taken to apply the tests under identical conditions as far as was possible. It was found that the pain or discomfort of undue traction or pressure on the tongue by the controlling fingers interfered with the finer appreciations of taste; dryness of the tongue prolonged the normal latent interval and that it was difficult to place the materials on areas which correspond exactly.

Test 2.—The materials were placed on the tongue as in *Test 1,* the patient was then allowed to withdraw his tongue into his mouth, but was asked to keep the materials confined as far as possible to the experimental areas under test and not to allow them to be freely washed about the mouth with saliva.

The obvious fallacy of the test is that the materials go into solution in the saliva and so diffuse on to areas of the mouth which are not under test at that time. The patients, however, are aware of this, but are able to analyse the sensations coming from the two sides or front and back of the tongue with useful precision, and with results very similar to those just recorded.

Results :—

Taste was completely lost in	2 cases
Taste was delayed 30 seconds or more in	32 cases
Taste appreciated in the same time as on the normal side in ...	6 cases

Test 3.—All the patients were given alternatively salt, sugar, vinegar and quinine asked to take them into the mouth in the ordinary way and to describe in detail the sensations aroused on each side of the tongue and palate.

Results—Thirty-eight people out of forty were certain that taste for salt, sour, bitter, sweet was impaired on the anæsthetic part of the mouth. Taste was fainter and far less crisp than on the sensitive side and a great effort or concentration was necessary before the substance could be named.

From three patients the following unprompted statements were obtained when it was suggested to them that no change in their powers of taste could possibly have followed their operations:—

(1) One woman said that her doctor was giving her a medicine with a nasty taste, she took this on the anæsthetic side of the tongue and she did not taste it until it reached the back of the throat.

(2) A woman fond of sweets said she could taste an acid drop on the sensitive side of the tongue only.

(3) A man whose tongue was bilaterally anæsthetic in its anterior two-thirds, said that he used to salt his porridge very heavily at first, but soon had to cut it down, because, when the porridge reached the back of his throat, it produced an unpleasantly salty sensation.

Discussion.

From the historical section it will be seen that not only in the past, but in the present century, neurologists and neuro-surgeons have expressed many conflicting views on the changes in taste following trigeminal denervation of the mouth. Dandy (1930) stated categorically that no change follows trigeminal root section, whereas Harris believed that changes are usual and that they are permanent when the third division or Gasserian ganglion are destroyed with alcohol. It seems difficult to reconcile two views so diametrically opposed; there must be some reason for this divergence of opinion and it is of interest to inquire what this may be.

The physiological mechanisms of buccal taste are best set into action with the tongue inside the mouth, with the lips closed and with the substance freely washed with saliva pressed firmly against the palate. Until these conditions are satisfied it is difficult to analyse the finer appreciation and discrimination of taste. In the usual tests with the tongue in the extruded position the conditions are abnormal and if the time factor is used as the only measure of gustatory change the cruder losses only are found and the more delicate changes are likely to be overlooked. This fact was realized very early in the present study and so was given particular consideration in the assessment of the results. When the patient first discovers that one side of the tongue is numb he is apt to assume that sense of taste has also gone from the anæsthetic area and gives his answers accordingly. Therefore, it was deemed advisable to explain the anatomical problem to each patient before his opinion was finally accepted; if this had not been done a far greater number would have been found in the group of complete loss immediately following operation.

There is no doubt in the author's opinion that trigeminal denervation of the tongue and mouth does affect the powers of buccal taste but more particularly in a discriminating way than as an absolute loss. These discriminative changes are more definite when both the 3rd and 2nd divisions are affected than when the 3rd division alone is blocked, an observation which very clearly demonstrates the importance of the soft palate as a receptor of gustatory stimuli.

Dandy, by a series of precise neurectomies in the posterior fossa, has proved beyond doubt that the glossopharyngeal nerve and the pars intermedia Wrisbergii are the anatomical pathways of buccal taste; when these nerves are severed the power to appreciate the tastes of salt, sour, bitter, sweet disappears absolutely.

It seems strange that trigeminal denervation should affect the sense of buccal taste, as it certainly does, when the 5th nerve is not one of the gustatory pathways. The changes in taste in the large majority of cases cannot be accounted for by damage to the great superficial petrosal nerve because they are present after the trigeminal root has been divided in the posterior fossa where the great superficial petrosal nerve is far from possible injury. Moreover, in those cases where the great superficial nerve was severed deliberately the gustatory changes were no more pronounced than in those cases in which it was conserved. The petrosal route for the taste fibres from the anterior two-thirds of the tongue may account for loss of taste in some cases but it has to be realized that this alternative route is rare whereas the impairment of taste following trigeminal denervation of the mouth is usual. As the gustatory pathways do not pass through the posterior root of the trigeminal nerve and as the changes in taste cannot always be accounted for by injury to the great superficial petrosal nerve there must be some other reason to account for the gustatory loss following trigeminal denervation.

The loss of feeling in an anæsthetic face is objective only; subjectively the face is full of feeling; numbness is a very outspoken sensation indeed, it embraces at least two components, coldness and swelling, and the feeling of swelling may be so dominant that it may be difficult to persuade the patient that there is no visible or palpable swelling. There is a decidedly unpleasant quality in the sensation of numbness and if not exchanged for that of painlessness the patients complain bitterly; a numb painful face is more unpleasant than a sensitive painful face.

It is unlikely that the sensation of numbness is due to stimuli arising in the severed nerve because pain would almost certainly be present if the cut proximal end were generating impulses. The sensation of pain is always absent following root section in cases of tic douloureux. It may be objected that impulses arising in the cut proximal end of the nerve do not give rise to the same sensations as run up the nerve when it is in connection with its receptors. The argument can be settled with some certainty when operating under local anæsthesia as any stimulation of the proximal nerve fibres causes a sensation of pain and not one of numbness. Moreover, a sense of numbness is caused irrespective of the method used for blocking the nerve impulses whether it be section, injection of alcohol or destruction of the nerve fibres by a diathermy current. It is improbable that such different local interferences with the nerve would initiate identical stimuli.

When the trigeminal nerve is cut the face is not completely denervated, there still remain intact the facial nerve, the autonomic nerves and the hypoglossal nerve. The sense of numbness may be due to sensations arising in the autonomic system or in the mechanisms of deep sensibility. Numbness, however, is still present when the facial nerve is out of action and is not removed by stellate ganglionectomy.

Normal sensation most likely is the summation or integration of all sensations normally coming from the face; if one modality is removed, then, even though each of the remaining modalities of sensation remains intrinsically unaltered they will not be able to stimulate the sensorium in the normal way. It may be suggested, therefore, in interpreting the changes in sensation of taste, that there is a readaptation of the higher centres to a new and unaccustomed combination of sensory impulses. In the case in question the taste impulses lack the background of common sensations.

III.—The Innervation of the Cornea.

Marshall (1931), after reviewing Jefferson's cases of fractional root section, came to the conclusion that the cornea had a dual nerve supply, the upper half being supplied by the ophthalmic division and the lower half by the maxillary division of the 5th nerve. The observations on the present series do not confirm this view. In four cases of intracranial section of the maxillary nerve at the foramen rotundum the upper boundary of anæsthesia skirted the rim of the lower eyelid and in no case did it encroach on the cornea. To confirm this finding a clean anatomical severance of the ophthalmic fibres was necessary. This section was carried out successfully on a suitable case, in which the pain was limited to the forehead, after intracranial reflection of the dura mater upwards from the margin of the sphenoidal fissure. The whole of the cornea was rendered insensitive by the neurotomy and it is believed that this is the first time this observation has been made in man.

Whether the cornea is supplied by pain fibres alone has long been a subject of discussion amongst anatomists and neurologists and until a small series of five patients had been operated on by the Sjöqvist technique a confident opinion could not be expressed on this neuro-anatomical problem. In the Sjöqvist operation the descending fibres of the trigeminal tract are divided in the medulla oblongata at the level of the first vagal root; this method of tractotomy renders the face analgesic, sensibility to light touch being impaired to a slight degree only. In two cases in which the section had been carried out with precision the cornea was completely insensitive to all kinds of painful stimuli but appreciated the stimulus of a wisp of wool, or the touch of a fine camel hair brush. Marshall also showed that the cornea was sensitive to light touch as well as to painful stimuli and in explanation suggested that the nature of the sensation aroused depended on the form of the stimulus, a sufficiently light one invoking the sense of light touch and a heavier one a sense of pain. This physiological explanation is unnecessary, since the dissociated anæsthesia produced by the trigeminal tractotomy offers a ready anatomical solution. The sense of touch is ordinarily in abeyance because it is overwhelmed by the sense of pain.

IV.—THE MOVEMENTS OF THE TONGUE.

That the smooth co-ordination of the movements of the tongue depends in large measure on impulses mediated by the trigeminal pathways has been demonstrated by two cases of bilateral nerve section. In each case immediately following the second operation, the tongue became ataxic, it came forward between the teeth whenever the patient attempted to speak, enunciation of long words was uncertain and the tongue could not be held still in the position of protrusion. The ataxia improved considerably with time, although there had been no regeneration of the divided nerves. This probably indicates that, as in the facial nerve, there are also proprioceptive fibres in the hypoglossal nerves, which though not so important as those in the trigeminal nerve, are able when necessary to function usefully. A considerable degree of compensation occurs, but is generally incomplete. The slight spitting of these patients in conversation and the slight difficulty of their enunciation suggest a loss of proprioceptive sensation.

V.—CHANGES REFERABLE TO THE SYMPATHETIC NERVOUS SYSTEM.

Two methods for detecting interference with the sympathetic pathways in the face have been used, reflex sweating and the vascular tests. No temperature or colour change has ever been recorded in the anæsthetic skin following tractotomy, root section or intracranial neurectomy. They have been observed only when alcohol is being injected into the ganglion and were first commented on by Jefferson. The vessels in the conjunctiva dilate, the eyelids blush and the temperature rises about one degree on the galvanometric scale of the electrical thermometer. These changes do not necessarily indicate the presence of sympathetic fibres in the ganglion, though that may do so; they could be explained by the diffusion of alcohol on to the neighbouring sympathetic fibres around the carotid artery. One experience in a recent case rather favours this view, as shortly after the blush of the eyelids a transient 3rd nerve palsy developed, showing that diffusion of the alcohol was taking place. The flush can, however, be observed in cases where no extraganglionic complications occur.

The sweating tests have been studied in some detail. List and Peet were the first to carry out these tests after trigeminal denervation and they came to the conclusion that few or no sympathetic fibres join the trigeminal pathways within the cranial cavity, but that extracranially a rich supply of sympathetic fibres is given to the various trigeminal branches from the periarterial plexuses on the large vessels in the vicinity. List and Peet's intracranial sections are precise but their extracranial experiments necessarily lack precision and so are open to criticism. It is scarcely possible to resect or block the supra-orbital nerve without damaging such neighbouring structures as vascular plexuses. Neurectomy necessitates a fair sized incision and one can never be sure that an injection of alcohol into so small a nerve as the orbital remains entirely intraneural. In two cases in which a considerable length of the supra-orbital nerve had been avulsed several months previous to the test, and the forehead was still numb, the reflex sweating reactions were equal on both sides. It seems strange that if the main sympathetic pathways run in this nerve they should have made so complete a recovery as shown in these two cases. The results in the present series have not been so clear cut as those of List and

Peet. For instance, in one case it was impossible to make either the denervated side or the fully sensitive side of the face sweat even though the rest of the body and arms were sweating profusely. Also in some cases of posterior root section the sweating has been much more patchy on the operated than on the unoperated side; in the lateral extradural approach this might be accounted for by damage to sympathetic fibres outside the trigeminal root but similar differences have occurred in one case of root section through the posterior fossa where this possibility can be eliminated. What is certain, however, is that sympathetic fibres in any bulk do not enter the intracranial trigeminal pathways and in no case of tractotomy were the sweating reactions diminished. This indicates that sympathetic fibres are not present in the caudal parts of the trigeminal tract. Alternatively, there is no clear evidence that the sympathetic fibres follow accurately the peripheral branches of the trigeminal nerve.

VI.—The Great Superficial Petrosal Nerve: The Ætiology of Paralytic Interstitial Keratitis.

One of the most serious complications following ganglion block or root section is the development of paralytic interstitial keratitis. Recently, it has been suggested that the essential cause of keratitis is a dry eye, that is, the absence of tear secretion. This view is gaining ground and is influencing the mode of treatment. The anatomical pathway generally accepted for secretory nerves to the lachrymal gland is circuitous. The great superficial petrosal nerve leaves the geniculate ganglion of the facial nerve to enter the middle fossa via the hiatus fallopii, it is then joined by the deep petrosal nerves from the sympathetic plexus on the carotid artery to form the vidian nerve. This dual nerve traverses the vidian canal to enter Meckel's ganglion and from here a secretory nerve passes to the lachrymal gland via the temporo-malar branch of the second division of the trigeminal nerve.

As the dura mater is swept from the floor of the middle fossa in the operative extradural approach to the trigeminal root, the great superficial petrosal nerve is seen lying on the tip of the petrous bone and it is part of the operation to separate by sharp dissection the nerve from the dural envelope to which it is firmly attached. It can be appreciated how easily the nerve may be injured and how easily suppression of tears be produced. If a dry eye be the cause of corneal ulceration, then the essential cause of keratitis is injury to the great superficial petrosal nerve. The method of separation of the great superficial petrosal nerve from the dura is the same in all middle fossa operations and so the nerve is exposed to the same dangers of injury in fractional as in complete root section. As a result it must frequently be out of action in those cases in which corneal sensation is spared and yet we have never seen keratitis when the cornea remained sensitive. There is ample clinical support for the view that the essential ætiological factor of keratitis cannot be paralysis of tear secretion alone. Many of our cases have a tearless eye on the operated side with a healthy cornea. In one case operated on by the Sjöqvist technique a transient keratitis developed in an analgesic eye in which tear secretion was normal. The only constant finding in keratitis is analgesia of the cornea and there is convincing evidence that the principal factor in its production is trauma acting on an insensitive membrane. Certainly it was the oft-repeated attempts at elicitation of the corneal reflex in the tractotomy case which caused the corneal changes because as we ceased to apply the stimulus the condition improved and keratitis did not develop in the opposite eye, even though the corneal reflex had been elicited in the same way and on the same number of occasions. Tarsorrhaphy invariably cures or arrests the keratitis and it may recur on division of the synechiæ even though an interval of a year or two has elapsed since suture. The factor of infection

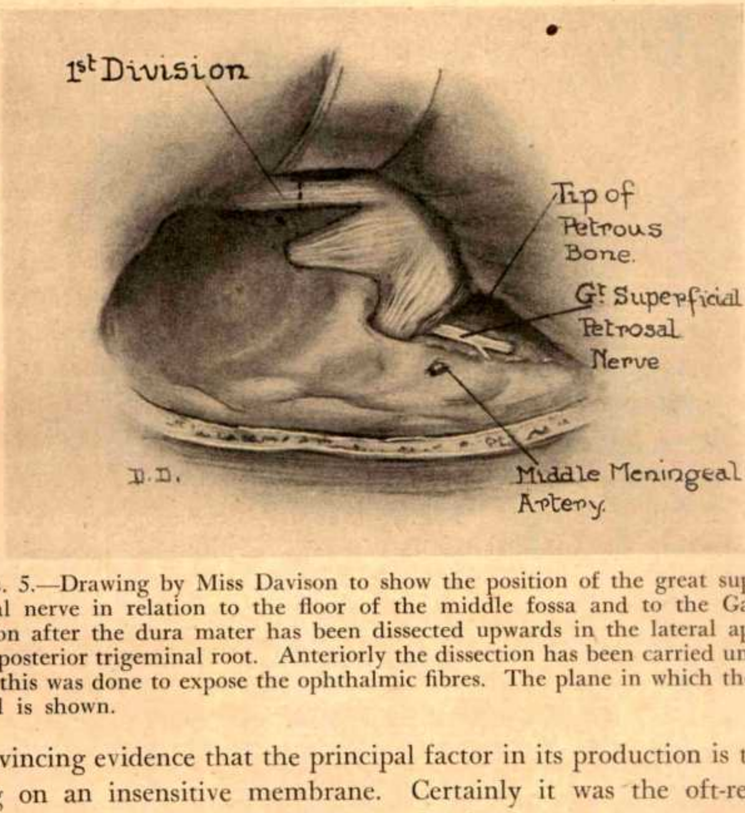

FIG. 5.—Drawing by Miss Davison to show the position of the great superficial petrosal nerve in relation to the floor of the middle fossa and to the Gasserian ganglion after the dura mater has been dissected upwards in the lateral approach to the posterior trigeminal root. Anteriorly the dissection has been carried unusually high ; this was done to expose the ophthalmic fibres. The plane in which they were severed is shown.

is apt to be overlooked and this is a grave danger. It must be the experience of every one that a pre-operative "bad eye" is particularly liable to be affected.

In addition to the clinical observations recorded above, experiments have been made in the course of section of the trigeminal root in the middle fossa. The great superficial petrosal nerve has been stimulated with a faradic battery on two occasions, it has been blocked once with alcohol and three times it has been divided with a scalpel. Faradic stimulation caused no marked increase in secretion of tears either early or late. In the cases of severance of the nerve tear secretion has later been stimulated emotionally and by the inhalation of pungent vapours (those from fresh horse-radish being found most useful) and the tears collected by a wisp of wool lying with its tail within the palpable fissure at the inner canthus. A serious criticism of this method of collecting tears is that the absorbent material in the sensitive eye is an adequate stimulus to tear secretion, whereas it has no such stimulatory action on the insensitive eye and so the measurement by weight, though theoretically more precise, is perhaps no more trustworthy than those of direct observation when the changes are sufficiently obvious. The results of these experiments show that when the pathways of the great superficial petrosal nerve are blocked or completely severed the secretory powers of the lachrymal gland are not entirely in abeyance, some other mechanism, probably a local one, takes over and though tear secretion is far from the normal the eye coverings are kept adequately moist.

In the final review of the ætiology of keratitis it has to be admitted that though analgesia of the cornea is an essential primary factor no case in which the coverings of the eye have remained healthy has ever been completely dry in spite of the absence of obvious tear secretion. To prove the essential part played by the lachrymal gland it is necessary to observe a completely dry eye with a normally sensitive cornea. Unfortunately it has not been possible to produce this combination and no record of one can be found.

Test No. 1.—Fractional Section by the Lateral Extradural Approach of the Upper Two-thirds of the Trigeminal Root with sparing of the Mandibular Fibres.

The great superficial petrosal nerve was dissected free from the dura mater and then severed with a scalpel. The cornea and conjunctiva were completely anæsthetic.

Result :—	R. Operated side	L. Normal eye
Weight of wool	0·1300 grammes	0·1275 grammes
Weight of wool + tears	0·1315 ,,	0·2850 ,,
Weight of tears in grammes collected in ½ hour	0·0015 ,,	0·1575 ,,

Comment.—In this case the insensitive cornea was perfectly healthy ; it was moist but tear secretion was absent ; free tear secretion was present in the sensitive eye.

When tears were made to secrete by emotional stimuli they welled into the sensitive eye, but few could be seen in the denervated eye. Before operation tear secretion was equal in both eyes.

Test No. 2.—Fractional Section by the Lateral Extradural Approach of the Lower Two-thirds of the Trigeminal Root with sparing of the Ophthalmic Fibres. The great superficial petrosal nerve was defined and then severed with a scalpel.

Result :—	R. Operated side	L. Normal eye
Weight of wool	0·2204 grammes	0·2010 grammes
Weight of wool + tears	0·2224 „	0·2126 „
Weight of tears in grammes collected in ½ hour	0·0020 „	0·0116 „

Comment.—The cornea and conjunctiva were healthy. The coverings of the eye were moist. Tear secretion was diminished.

Test No. 3.—The whole trigeminal root was severed by the lateral extradural approach and the great superficial nerve divided by a scalpel. The cornea and conjunctiva were completely anæsthetic.

Result :—	R. Operated side	L. Normal eye
Weight of wool	0·2100 grammes	0·2175 grammes
Weight of wool + tears	0·2175 „	0·3900 „
Weight of tears in grammes collected in ½ hour	0·0075 „	0·1725 „

Comment.—The insensitive cornea was perfectly health ; the coverings of the eye were moist but tear secretion was diminished. Before operation tear secretion was equal on both sides.

Conclusion.—The great superficial petrosal nerve is a mixed nerve, the afferent fibres being probably gustatory to the palate and the efferent fibres being secretory motor at least to the eye and nose.

The above section is a preliminary note on work which is being done on the anatomy and function of the nerve and further results will be published later. I would like to thank Mr. Jefferson for the generous use of his material and for his criticisms and help in the production of this paper.

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THE CONGENITAL FACIAL DIPLEGIA SYNDROME: CLINICAL FEATURES, PATHOLOGY AND ÆTIOLOGY.[1]

A REVIEW OF SIXTY-ONE CASES

BY J. L. HENDERSON

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CONGENITAL paralysis of cranial nerves is sufficiently rare to attract special attention. The ocular and facial nerves are those most frequently affected and the anatomical relationships of the latter render them susceptible to paralysis from a greater variety of causes. Thus, there are several types of congenital facial palsy. The intra-partum types predominate and, with the extremely rare exception of bilateral peripheral trauma, they are all unilateral. Of the ante-partum types, however, the bilateral variety is the commonest and is usually associated with other cranial nerve palsies. This paper is solely concerned with the ante-partum bilateral type.

A child displaying many typical features of the condition was seen recently at the Royal Edinburgh Hospital for Sick Children. Perusal of the relevant literature showed that no adequate review of the published cases had ever been undertaken; German literature proved to be the most fruitful, while British literature contained brief accounts of only six cases. An analysis of the clinical and other features of this remarkable congenital syndrome may, therefore, be of interest.

CASE REPORT.

E. O., female, aged 1 year 10 months.

History.—The parents, a sister aged 12 and a brother aged 8, are healthy. The pregnancy was normal. Spontaneous delivery followed an uneventful labour lasting nine hours. The birth weight was about eight pounds. A peculiar facial appearance, bilateral convergent strabismus and club-foot were all noticed shortly after birth by the doctor in attendance. The baby apparently nursed quite well, although her mother maintains that she did not nurse as well as her other children. She was weaned when two months old. There was never any dysphagia nor nasal regurgitation.

The patient first came under observation at the age of 5 months, her mother complaining that she had never smiled nor moved her face—even when laughing and crying. During the first few weeks she thought the infant had a film over her eyes and that she was blind. She did not seem to take notice until she was 3 months old. When first seen the infant was well nourished and displayed an immobile, expressionless face, a severe degree of bilateral convergent strabismus and a partially corrected talipes equino-varus on both sides. There was no ptosis and the eyes were not completely closed during sleep.

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[1] Based upon a thesis accepted for the degree of M.D.Edin., July, 1938.

As the child grew older the eyelids became more nearly approximated during sleep, and a slight but definite amelioration of the squint was observed. Recently, while eating, she had been observed to dislodge food from the cheeks with her hands. Early doubts about the mental state were soon dispelled as the child grew older. Orthopædic measures, begun soon after birth, effected a great improvement in the position of the feet. Dentition began at 5 months. Apart from a recent mild attack of bronchitis the general health has been good.

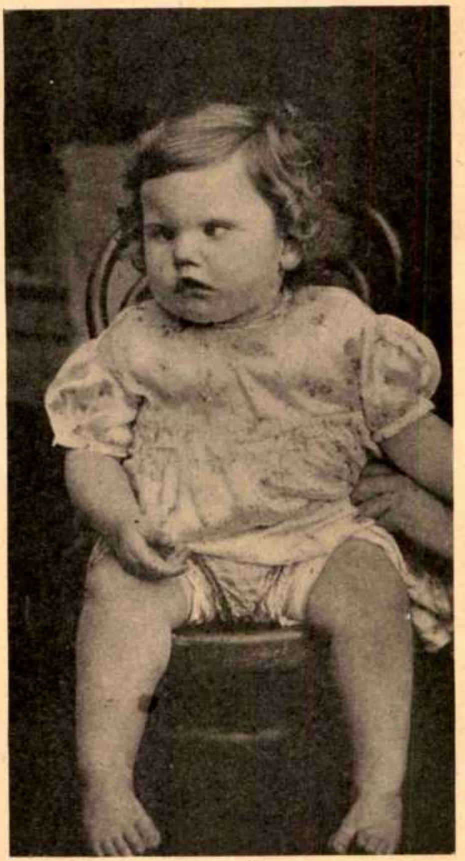


FIG. 1.—E. O., aged 1 year and 5 months.

Physical examination.—A healthy looking, well-developed female child. The forehead is tower-shaped and somewhat flattened towards the sides ; the fontanelle is almost closed. The cheeks are plump and the peri-orbital regions rather hollow.

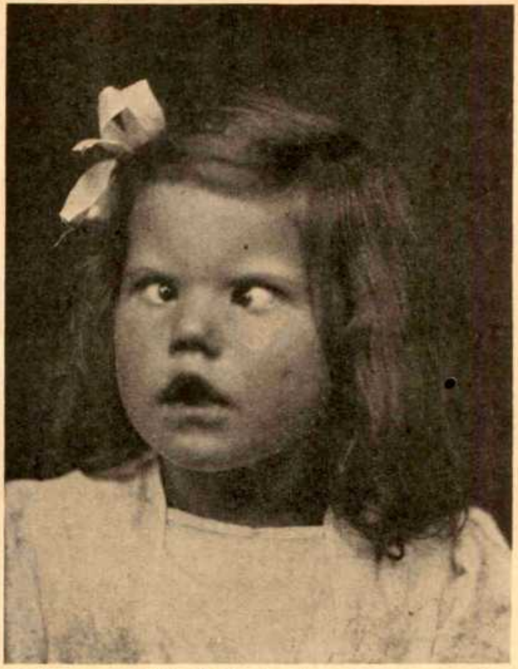


FIG. 2.—E. O., aged 3 years. "Smile" showing the contraction at the left corner of the mouth.

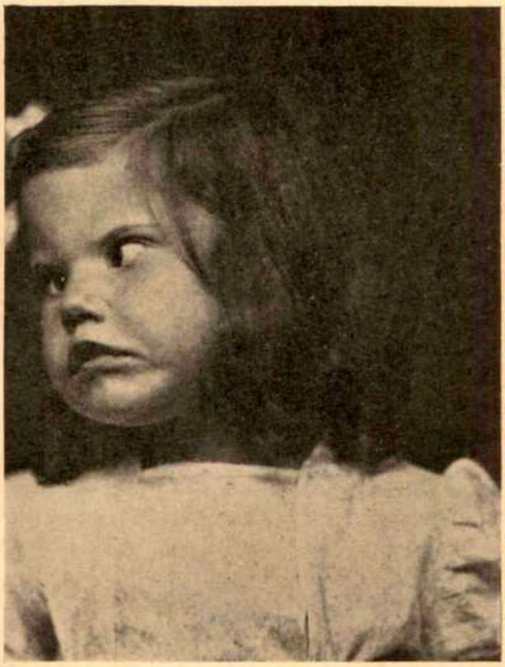


FIG. 3.—E. O., aged 3 years. Crying.

There is bilateral epicanthus. The base of the nose is broad and the lower part has a squarish appearance owing to the palsied alæ nasi. The mouth is always slightly open and the upper lip prominent ; during sleep it is opened more widely and assumes a triangular shape. The uvula is normal. The ears have a normal shape. There is no malformation of the pectoral or mammary regions. The only deformity of the limbs is the bilateral talipes equino-varus. The mental development and behaviour are normal.

Cranial nerves.—The 3rd, 4th and 6th nerves: When looking at objects the head is moved in the direction of vision, whether horizontal or vertical, and it is usually tilted to one or other side. I am indebted to Dr. J. R. Paterson, Hon. Ophthalmic Surgeon to the Royal Edinburgh Hospital for Sick Children, for the following report on the condition of the eyes:—

" There is a severe degree of convergent strabismus in both eyes. The only definite movement that can be elicited is the involuntary upward movement of the eye on the child attempting to close the lids. It would, therefore, appear that the superior rectus is still functioning in both eyes, certainly as far as this synergic movement is concerned. There is no ptosis, indicating normal action of the levatores palpebrarum ; the lids are now approximated during sleep. The pupils are normal in size, shape and reactions. The fundi show no abnormality whatever."

The 7th nerve: The face is immobile and expressionless at all times, indicating complete facial diplegia (fig. 1). There are no wrinkles in the skin of the face or forehead. Winking is slow and feeble and there is a moderate degree of epiphora. A little dribbling occurs from the corners of the mouth. Crying produces a whining noise with the usual interjections, and laughter a series of short, pleasant phonations. The former is accompanied by flushing of the face, but there is no facial movement in either. The vocabulary consists of only a few simple words and enunciation is hampered by the labial palsy. No response of the facial muscles to either faradism or galvanism could be obtained, but the child's nervousness rendered accurate testing of the muscles impracticable.

Other motor nerves: There is no evidence of paresis in the muscles of mastication or in the soft palate, pharynx or larynx. The child cannot be induced to protrude the tongue beyond the lips, but there are no signs of lingual atrophy or palsy or of fibrillary twitching.

Sensory nerves: There is no apparent impairment of any of the sensory functions.

There are no other demonstrable abnormalities of the nervous system.

Other systems.—The thoracic and abdominal organs appear healthy.

X-ray examination: The skull has a tower-shaped frontal region, but is otherwise normal. The vertebral column is normal.

Blood Wassermann: Negative.

Further examination.—Aged 3 years 1 month.

The parents first noticed a slight movement of the left corner of the mouth when the child was 2½ years old, and they maintain that its amplitude has increased. She often " smiles " when asked to do so and the parents' observation is easily confirmed. The movement is small but is accompanied by considerable wrinkling of the skin infero-lateral to the left side of the lower lip (figs. 2 and 3). No other facial movement is discernible.

There is no longer any doubt about the condition of the lingual muscles as the tongue is frequently well protruded and has a normal appearance. The condition of the eyes is unchanged. The position of the feet has become worse owing to neglect.

The child is running about and has an attractive, friendly manner. Although she did not walk alone or speak freely until she was 2½ years old there is no question of any mental defect. Her vocabulary is good but it is difficult for strangers to understand much of what she says owing to the poor enunciation.

Summary.—Congenital facial diplegia, incomplete in left lower quadrant. Congenital ophthalmoplegia externa, bilateral, partial. Congenital talipes equinovarus, bilateral.

CLINICAL FEATURES.

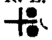
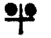
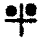
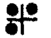
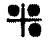
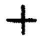
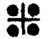
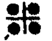
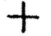
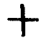
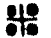
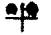
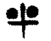
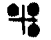
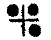
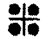
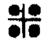
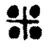
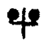
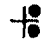
Since von Graefe described a case of congenital facial diplegia in 1880 some sixty examples of this anomaly have been recorded, and these, including the present one, have been tabulated in chronological order in Table I (pp. 386-8) where the principal clinical features have been indicated symbolically in each instance. The incidence of these features has been shown schematically in Table II (p. 389).

The facial diplegia is usually accompanied by palsies of other cranial nerves—particularly the ocular. The abducens nerves are affected in a high percentage of cases, the hypoglossal and oculo-motor nerves only in a minority. All these congenital palsies are, of course, stationary from birth. The high incidence of congenital deformities is also a striking feature: the chief of these is club-foot, while brachial deformity and pectoralis muscle hypoplasia have been observed on numerous occasions. Other malformations of a minor nature are frequently encountered. This outline of the principal features will now be followed by their individual consideration.

The facial diplegia.—The facial palsy was usually observed during the first few days of life owing to difficulty with nursing and incomplete closure of the eyelids during sleep. Quite often, however, it was not noticed for a few weeks or months, until the inability to smile or the lack of facial movement on crying aroused the parents' concern. The most arresting feature of the facial palsy was, of course, the mask-like face which was most noticeable during laughing and crying. Because of this immobility the face and forehead were devoid of wrinkles, but it was exceptional for the subcutaneous tissue or the skin of the face to appear "atrophic."

It is interesting that in some cases, as in the present one, a slight diminution in the width of the palpebral fissures during sleep was noticed as infancy advanced. Lagophthalmos was, of course, another feature and the principal cause of the incomplete palpebral closure. The puncta lachrymalia were frequently slightly everted, thus accentuating the

TABLE I.—PUBLISHED CASES OF CONGENITAL FACIAL DIPLEGIA SHOWING THEIR SALIENT CLINICAL FEATURES.

Case No.	Year	Authors	Sex	Age	Facial palsy, distribution ● = Complete	Abducens palsy		Convergent strabismus	Ophthalmoplegia externa		Ptosis	Trigeminal palsy		Lingual palsy		Mental defect	Club-foot		Brachial malformation		Pectoralis muscle defect		Other malformations, &c.
					R. L.	R.	L.		R.	L.		R.	L.	R.	L.		R.	L.	R.	L.	R.	L.	
1	1880	v. Graefe	M.	20		+	+																Epilepsy
2	1881	Harlan	M	18		+	+	+															
3	1882	Chisolm	F.	35		+	+	+															Aplastic lachrymal caruncles
4	1888	Moebius	M.	50		+	+												+				
5	1889	Schapringer	F.	8		+	+					+			+					+			Hypoplastic lachrymal caruncles. Bifid uvula. Epicanthus "Other abnormalities"
6	1891	Bloch	M.	$\frac{9}{12}$		+	+										+	+					
7	1892	Fryer	M.	16		+	+												+				
8	1895	Kirmisson	M.	7													+	+					
9	1896	Procopovici	M.	18																			
10	"	"	F.	7		+	+	+															Epicanthus
11	1897	Schmidt	M.	6		+	+	+						+	+						+		
12	1898	Thomas	M.	21																			Ear deformity. Deafness
13	"	"	M.	19																			Ear deformity. Deafness
14	1900	Heubner	M.	$1\frac{7}{12}$		+	+	+							+								No tear secretion
15	1901	Bernhardt	M.	$\frac{10}{12}$																			
16	1902	Koster	M.	?																			Ear deformity. Complete facial anhidrosis
17	"	"	M.	?																			Ear deformity. Complete facial anhidrosis
18	"	Decroly	M.	$\frac{7}{52}$					+	+													
19	"	Taylor	M.	15							+												
20	1903	Rainy and Fowler	F.	$\frac{10}{52}$																			

21	1905	Batten	?	9	?	+	+							+	+								
22	„	Gierlich	F.	14	●● +	+	+	+							+								
23	„	Gützmann	M.	12	●● +	+	+										+	+	+				Hypoplastic mammæ. "Other abnormalities"
24	1908	Ziehen	M.	18	+ ●●	+	+		+	+	+			+	+							+	
25	1909	Collins	?	?	?	+	+		+	+					+							+	
26	1910	Lennon	M.	2	●● + ●●	+	+	+	+	+							+	+					
27	„	„	M.	14	● +	+	+	+	+	+							+	+					
28	1912	Peritz	M.	?	?	+	+									+						+	
29	„	Welde	F.	2½	●● + ●●	+	+	+						+	+	+							
30	1913	v. Pfaundler	?	1/12	?	+	+							+				+					
31	„	Beetz	F.	22	+																+		Ear deformity. Congenital dislocation of hip
32	„	„	M.	20	+	+					+	+	+			+							Ear deformity. Multiple bilateral defects of scapular muscles
33	„	„	F.	7	+		+																Ear deformity
34	1915	Snowball	F.	11	●● + ●	+	+	+															
35	1916	Kahlmeter	M.	38	●● +				+	+						+							Infantilism
36	1917	Gütermann	M.	7/12	●● +	+	+	+						+					+		+		Hypoplastic lachrymal caruncles. Epicanthus
37	1918	Fry	?	11/12	+																		
38	1919	Fry and Kasak	F.	11	●● +	+	+		+	+		+	+	+	+					+		+	
39	1921	Abrahamson	F.	4	+	+	+								+								Epilepsy
40	1922	Cadwalader	F.	13	●● + ●●																		Deafness
41	„	„	F.	10	●● +	+	+	+															
42	1923	Kirby	M.	52	●● +	+	+							+	+		+						
43	1924	Cameron	M.	3	●● + ●●	+	+		+	+							+	+	+				
44	1927	Van Gelder and Weyl	M.	53	●● + ●●	+	+		+	+	+	+	+	+					+	+			Ear deformity

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TABLE I.—PUBLISHED CASES OF CONGENITAL FACIAL DIPLEGIA, &c.—*Continued.*

Case No.	Year	Authors	Sex	Age	Facial palsy, distribution ● = Complete		Abducens palsy		Convergent strabismus	Ophthalmoplegia externa		Ptosis	Trigeminal palsy		Lingua palsy		Mental defect	Club-foot		Brachial malformation		Pectoralis muscle defect		Other malformations, &c.
					R	L	R.	L.		R.	L.		R.	L.	R.	L.		R.	L.	R.	L.	R.	L.	
45	1928	Mandels	M.	15	?		+	+	+	+	+						+				+		+	
46	1929	Bonar and Owens	M.	$\frac{9}{12}$	● ●	● ●						+							+			●		Epicanthus
47	1930	Alajouanine, Huc and Gopcevitch	F.	6	● ●	● 	+	+	+									+	+	+				
48	,,	,,	F.	5	● 	● ●	+	+	+						+	+		+	+					
49	,,	,,	M.	$1\frac{9}{12}$	● ●	● ●	+	+	+									+	+					
50	,,	,,	F.	$\frac{4}{12}$	● ●	● ●	+	+	+									+	+					
51	,,	Ullrich	F.	8	+							+												Hypoplastic mammæ. Pterygium colli
52	1931	Yealland	F.	16	+		+	+		+	+				+	+								
53	,,	Spatz and Ullrich	M.	$\frac{3}{12}$	● ●	● 	+	+		+	+										+			Hyperthelia
54	,,	Allen	M.	10	● ●	● ●	+	+		+	+							+	+	+	+			Hydrocephalus. Epilepsy
55	1932	Bielschowsky	F.	9	● ●	● ●	+	+																
56	,,	Garrahan and Cucullú	M.	2	● ●	● ●	+	+	+									+	+					
57	,,	,,	F.	$\frac{2}{52}$	● ●	● ●	+	+	+						+	+		+	+		+			Bifid uvula. Epicanthus
58	,,	Babonneix and Miget	F.	5		● ●	+	+	+	+	+				+	+								
59	1933	Gareiso and Barbieri	F.	5	● ●	● ●	+	+	+								+	+	+					
60	1935	Decourt and Perreau	M.	9	● 	● 	+	+	+									+	+					
61	1939	Author's case	F.	$3\frac{1}{12}$	● ●	● 	+	+	+	+	+							+	+					Epicanthus
							45		23	15		6	4		18		6	19		13		8		

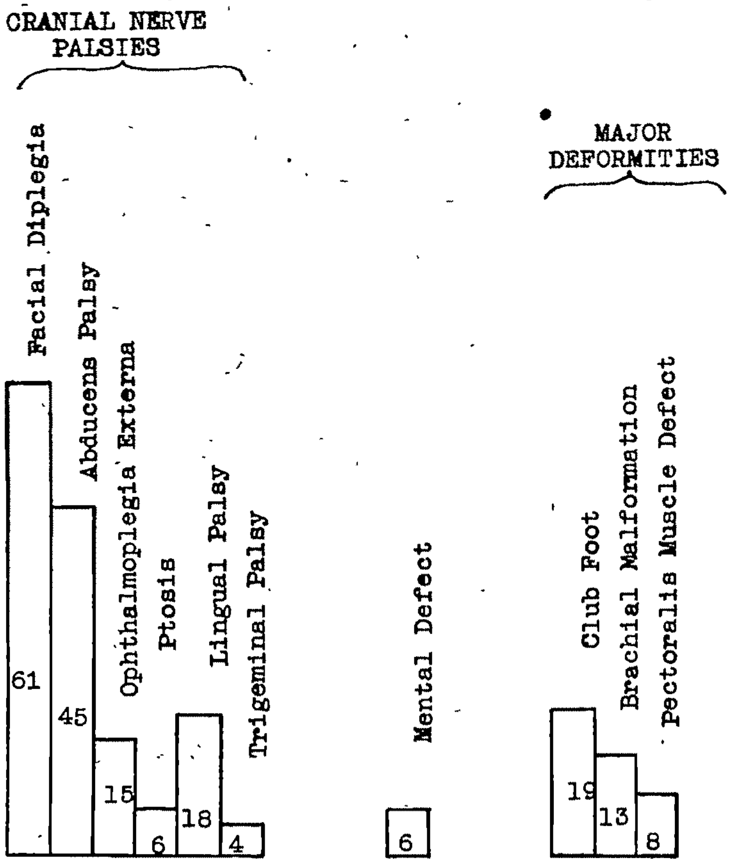
The following cases were inadequately authenticated for inclusion, but appeared to be genuine: Procopovici (1896), Treacher Collins (1915), Cadwalader (1922), Ullrich (1930), Errecart (1930).

The facial diplegia appears to have been acquired in the cases published by Recken (1891) and Bach (1893).

epiphora which was an almost constant feature. In older patients ectropion was apt to occur.

Inability to suckle in infancy has already been alluded to: the difficulty may be only slight, but it was often noticed that the nipple or teat was drawn further into the mouth than usual. Inability to close the mouth was the rule. Undue prominence of the upper lip was a striking feature; in adults the lower lip was usually everted and prominent also. Dribbling of saliva was a troublesome symptom. Speech was nearly always indistinct owing to the inability to close the lips and thus make labial sounds, e.g. ā for ma, ă for map. While eating, food was apt to lodge in the cheeks, as in the present case.

TABLE II.—INCIDENCE OF THE PRINCIPAL CLINICAL FEATURES



The degree and distribution of the palsy have been analysed in fifty-six cases, five being discounted owing to insufficient data. The palsy was incomplete in the majority of cases, but of severe degree in nearly all of them. Table III indicates the frequency of complete paralysis in each of the four facial quadrants. The diplegia was complete in one-third of the cases, and another third exhibited complete upper facial palsy. When partial it was usually asymmetrical, though the difference was rarely more than slight; it was complete on one side in ten cases. In a further ten cases no quadrant was completely paralysed. A more detailed analysis of the distribution is impracticable owing to the custom of describing the movements of the face in terms of regions rather than of muscles. It is clear, however, that those muscles which draw the corners of the mouth outwards and downwards, including the platysmæ, are the muscles which most frequently escape. The frontalis muscles are those most constantly paralysed; the peri-orbital muscles are usually completely paralysed also, but occasionally contain a few functioning fibres. It is unusual for any of the muscles to escape completely, and the degree of paresis is nearly always severe.

TABLE III.—DISTRIBUTION OF COMPLETE PARALYSIS IN THE VARIOUS FACIAL QUADRANTS.

R. L.	No. of cases
	19
	5
	4
	13
	1
	3
	1
	10
Not stated	5

● = Complete palsy.

The electrical reactions of the facial muscles were tested in twenty-three cases. There were no qualitative changes in the paretic muscles but a diminished reaction was invariable.

The characteristic distribution of the palsy contrasts sharply with that of the common supranuclear and infranuclear types, and it may be of diagnostic value in the absence of the other features of the syndrome.

Only ten cases of the sixty-one were uncomplicated by other cranial nerve palsies, and it may be significant that deformities of the limbs seldom occurred in this group. The incidence of the principal features in this group is contrasted with that in the " complicated " group in Table IV. The features of the facial palsy are usually similar in both groups.

TABLE IV.—THE CONTRASTING FEATURES OF "COMPLICATED" AND "PURE" FACIAL DIPLEGIA.

	Other cranial nerve palsies	No other cranial nerve palsies
Number of cases	51	10
Major deformities	28	1
Minor deformities only, excluding auricular	7	0
Auricular deformity	4	4
Deafness	0	3
Mental defect	6	0

Ocular manifestations.—In those with convergent strabismus the ocular abnormality was usually noticed at birth or shortly afterwards. In the absence of a squint, ocular palsies sometimes escaped notice until later infancy. The parents were often concerned by the white appearance of the eyes seen between the incompletely closed lids during sleep. This appearance is sometimes attributed to " a film over the eyes " as in the present case. A slight amelioration of the convergent strabismus was observed in three of the cases of Alajouanine, Huc and Gopcevitch (1930) and I am quite satisfied that it occurred in the present case also.

External ocular palsies, including ptosis, accompanied the facial diplegia in fifty cases—five-sixths of the total.

Abducens paralysis occurred in no fewer than forty-five patients, thus constituting one of the most characteristic features of the syndrome; it was bilateral in all except two cases and was usually complete. Abducens paralysis was the only ocular palsy in thirty-one cases ; it was accompanied by oculo-motor palsy in thirteen instances. Twenty-three—almost exactly half—of the abducens group had a convergent strabismus which was usually bilateral. It may be recalled here that strabismus is the rule in the acquired form of 6th nerve palsy. The absence of strabismus is usually associated with paresis of the medial recti muscles.

External ophthalmoplegia occurred in fifteen cases and was always bilateral; it was usually severe but rarely complete—it was thought to be complete in the infant described by Spatz and Ullrich (1931). Internal ophthalmoplegia has never been observed.

Ptosis occurred in six cases; it was usually only partial, but it was bilateral in each instance. In three cases it was the only ocular palsy to accompany the facial diplegia, in another it complicated a slight unilateral abducens paresis, while in the remaining two cases it was associated with ophthalmoplegia externa.

Trochlear involvement has seldom been referred to in the literature, probably owing to the difficulty of assessing it—especially in children—but this nerve is liable to be affected along with the oculo-motor nerve as demonstrated histologically by Spatz and Ullrich in their case.

Amblyopia was not a feature of these cases, but refractive errors and astigmatism frequently occurred.

Owing to the feebleness of winking and the incomplete closure of the eyelids during sleep the corneæ and the conjunctivæ are poorly protected, and recurrent or chronic conjunctivitis frequently occurs. Corneal opacities are unusual but are sometimes seen in adult patients.

Lingual features.—Paresis and hypoplasia of the tongue occurred in eighteen cases and was always associated with ocular palsy. It involved both sides in ten cases but was rarely symmetrical. Fibrillary twitchings of the tongue were noted in two instances, but no significance can be attached to them in view of the static condition of the lingual and other palsies from birth. The dysarthria and the difficulty in moving food about the mouth were accentuated by lingual involvement.

Trigeminal palsy.—It was unusual for the muscles of mastication to be affected, but in four cases masticatory difficulty was encountered. It affected both sides in three of them but was never severe. The striking feature was the restriction of lateral chewing movements.

Paresis of the soft palate.—In many of the cases no reference was made to the throat, presumably indicating normal findings in most of them. There were four instances of bilateral paresis of the soft palate, six of dysphagia—in three of which it recovered in infancy—and four of nasal regurgitation in infancy. Three of the cases with dysphagia and regurgitation had lingual palsy which probably contributed to the difficulty. In no case was there any evidence of gross vagal dysfunction: the nerves responsible for the paresis of the soft palate are distributed via the vagus nerve but originate in the accessory nuclei.

Club-foot.—The malformation occurred in nineteen cases—almost one-third of the total—and it was bilateral in sixteen instances. The deformity was one of talipes equino-varus in all cases except that of Kirmisson (1895) which had the usual deformity on the right side and a calcaneo-valgus deformity on the left. In most of these cases the deformity had been partially or wholly corrected in infancy. Other deformities of the foot, such as syndactyly, have never been recorded.

Pectoralis muscle defect.—Hypoplasia of the pectoralis muscles was a feature in eight cases; it was always unilateral and associated with mammary hypoplasia of the same side. The condition was described in detail in only three cases and was typical of congenital defect of the pectoralis muscles. All three patients showed a complete absence of the sterno-costal part of the pectoralis major, while the clavicular part was only slightly affected or had escaped altogether; the pectoralis minor was absent in two cases and hypoplastic in the third. In the case described by Mandels (1928) the 3rd, 4th and 5th costal cartilages were defective, and the hypoplasia involved other muscles of the chest and arm on the corresponding side. The association of local skeletal anomalies with pectoralis muscle defect is not infrequent. In three cases there was brachial hypoplasia on the same side.

Mention may be made here of the unique case of Beetz (1913)—Case No. 32, a youth of 20 years whose pectoralis muscles did not appear defective, but who exhibited a hypoplasia of the serratus anterior, infraspinatus and latissimus dorsi muscles on both sides, and of the trapezius, levator scapulæ and supraspinatus muscles on the right side. The serratus anterior was completely absent on the right side and poorly developed on the left. Bilateral muscle defect is a very rare anomaly.

Malformation of the arm and hand.—Brachial malformation was encountered in thirteen cases, in twelve of which it was specified; it involved the arm in only four instances whereas the hand was always affected. There was one instance of congenital amputation of the hand and one of "club-hand," while in four cases the affected hand was "much smaller" than the other—syndactyly was a feature in two of these cases. In the six remaining cases the malformation was confined to the fingers; in two there were brachydactyly and syndactyly, in three others there was syndactyly alone, while another possessed a deformed index finger. The syndactyly was bilateral in two of the seven cases in which it occurred. Three of the four cases with brachial malformation exhibited pectoralis muscle defect on the same side, whereas none of the nine cases with hand involvement alone was so affected. The brachial dysplasia was associated with club-foot in five cases.

Minor congenital anomalies.—In a few instances these have been disposed of as "other abnormalities," but in the great majority they have been enumerated. In several cases the root of the nose was broad and rather flat. Bilateral epicanthus occurred in six cases, in two of which it was associated with hypoplastic lachrymal caruncles. Another case had aplastic lachrymal caruncles. There were eight instances of ear deformity; it was usually bilateral and confined to the lobe: two of the three deaf cases fall into this group. Arched palate was noted four times and bifid uvula twice. In addition to those cases exhibiting pectoralis muscle defect, bilateral mammary hypoplasia occurred in two cases in which the pectoralis muscles appeared normal. Pterygium colli was a feature of Ullrich's (1930) atypical case.

Only a few cases exhibited functional anomalies which were probably congenital. Lachrymation was totally absent in Heubner's (1900) case ; this was also observed by Bernhardt (1894, 1897) in two cases with the analogous type of unilateral facial palsy. Sweat formation could not be stimulated on the face in the two siblings described by Köster (1920). The case of Kahlmeter (1916) presented several unusual features of uncertain nature, the chief of which were infantilism, vasomotor disturbances in the legs and a high sugar tolerance. Three cases were epileptic but none of them were regarded as mentally defective.

Mental defect.—In six cases there was clear evidence of subnormal mentality, four of these had reached adolescence or adult life and the other two were young children. The degree of amentia did not appear to be severe in any of these patients. A few other cases in infancy or early childhood were described as backward or possibly mentally defective. In assessing the mental state the retarding influence of the congenital palsies is apt to be misleading.

An analogous unilateral facial palsy.—A rarer type of congenital facial palsy is the unilateral variety which appears to be analogous to that under review. The palsy has the same distribution and characters as in the bilateral cases, but there is a greater tendency for it to be uncomplicated. Apart from abducens paralysis—which occurs in about half of the cases—cranial nerve palsies and structural defects of the limbs are infrequent. The abducens paralysis is usually bilateral, but occasionally only homolateral.

Amongst others, cases have been recorded by: Schultze (1892), Bernhardt (1894, 1897), Warrington (1897), Langdon (1899), Stéphan (1900), Minor (1900), Lagrange (1901), Comby (1901), Souques (1903), Babonneix and Miget (1932), Dupuy-Dutemps (1934) and Bálint (1936).

PATHOLOGY.

It is unfortunate that pathological evidence is available in only three of the published cases. They are those of Heubner (1900), Rainy and Fowler (1903) and Spatz and Ullrich (1931). The morbid anatomy and histology of these cases are of interest.

Heubner's case.—Male, aged 1 year and 7 months: died of bronchopneumonia. The chief clinical features were congenital facial diplegia, bilateral abducens palsy and left lingual hemiparesis. The facial palsy had remained unchanged from birth, it was complete on the left side and of typical distribution on the right side, the muscles at the corner of the mouth being incompletely paralysed. There was no spasticity of the limbs. The more delicate functions of nervous control could not be tested on account of the age and mental retardation.

The complete neuromuscular units of the affected parts were not examined, only the brain and spinal cord being retained. Macroscopically, the medulla oblongata was asymmetrical, the left half being smaller than the right, and some of the tissue underlying the pyramid had a shrunken appearance. The right and left optic and oculomotor nerves and the left trochlear nerve looked normal, but neither the right trochlear nerve nor the abducens nerves could be found.

Histologically, the most notable abnormalities were seen in the motor nuclei of the cranial nerves, especially in the 6th, 7th and 12th, and to a lesser extent, in the 3rd and 11th. The 6th pair showed the most striking changes, ganglion cells being almost completely absent in both nuclei. In the 7th and 12th pairs the left-sided nuclei were the more abnormal, but the right also contained a diminished number of ganglion cells. Corresponding to the decrease in the number of cells the roots of the nerves were lacking or sparsely developed. The left accessory nuclei showed similar changes. The 4th nuclei were not specially mentioned, but the 5th, the 9th and the 10th were normal. The anomaly was not limited to the nuclei however. The medial longitudinal bundle was very hypoplastic on both sides, this corresponding in degree and extent with the affection of the nuclei. The formatio reticularis was sparsely developed, particularly on the left.; the interstitial tissue was more affected than the nerve cells, but those nerve cells present were well developed. Both olives were hypoplastic, particularly the left, but the diminished number of nerve cells were normal in appearance. Further, on the left not only the fibres of the pyramidal tract streaming out from the motor nuclei appeared to be unusually sparse, but the whole pyramidal bundle, even in the lower part of the medulla, seemed to be under-developed. Marchi's stain failed to show any degenerative changes in the brain or cord.

Rainy and Fowler's case.—Female, aged 10 weeks: forceps delivery; died of broncho-pneumonia. The facial diplegia was almost complete, only slight contraction of a few medial fibres of the right frontalis muscle and drawing down of the right corner of the mouth being possible; there were no other nerve lesions and no structural anomalies. The whole neuromuscular unit of the 7th pair of nerves was examined. The brain and nerves appeared normal, but there was gross "atrophy" of the facial muscles.

Serial sections from the 2nd cervical segment to a point above the 3rd nucleus were examined. The only abnormalities seen were in the 7th nerves and their nuclei. Both nerves showed marked degeneration, the ascending part of the root, the fasciculus teres and the emergent portion alike. "In the nuclei a large number of the cells ordinarily present had disappeared whilst those which remained presented a distinctly atrophic aspect, their processes being poorly developed, the Nissl's bodies irregular and the cells themselves much smaller than one would have expected. The apparently healthy cells of the 6th nuclei afforded a marked contrast to those of the 7th." Like the roots, the nerve trunks showed advanced degeneration. The few fragments of muscle which could be found were normal histologically.

Spatz and Ullrich's case.—Male, aged 3 months: died of bronchopneumonia. The facial diplegia was complete apart from drawing down of the left corner of the mouth, and there appeared to be complete ophthalmoplegia externa. Syndactyly was the only other anomaly.

The pons and medulla oblongata were relatively small, but the pyramids and olives were normal. The 3rd and 7th pairs of nerves were very thin and the 6th was absent, but the others appeared normal. No naked-eye changes were seen in the hemispheres or brain-stem on sectioning.

Histological changes were seen in the 3rd, 4th, 6th and 7th nuclei. The 6th were the most severely affected, the nuclei were unduly small, but of normal appearance, and the roots were also small. The 4th nuclei were not in the usual place but were represented by scattered elements lateral to it; the root fibre bundles were very small. The nerve cells in the 3rd nuclei were reduced in number and the roots were correspondingly small.

Bálint's case.—Bálint (1936) reported the autopsy findings in an infant 3 months old with congenital 6th and 7th nerve palsy on the left side. The facial palsy was atypical, being incomplete in the frontalis and orbicularis oculi and the triangularis and mentalis muscles. Twitchings of the facial muscles were observed.

Histological examination revealed a degenerative process which involved both abducens nuclei, the left being almost completely destroyed and the right considerably damaged. The fasciculus teres of the left facial nerve was also disorganized, with secondary degeneration of the nucleus. No further details are given in the report.

Comment.—The similarity of the pathology in the cases of Heubner and of Spatz and Ullrich strongly supports the view that nuclear hypoplasia accounts for the cranial nerve palsies in all typical cases of the syndrome. Heubner's case with extensive nuclear lesions shows that a more diffuse hypoplasia of nervous elements may also occur. The degenerative changes in the 7th nerves and nuclei in Rainy and Fowler's atypical case of uncomplicated facial diplegia may have been due to forceps trauma of the facial nerves as suggested by Zappert (1910). It would seem reasonable to suppose that the pathology of some of the cases without multiple cranial nerve involvement or structural defects may also be of a similar nature. However, the fact that the distribution of the facial palsy usually corresponds with that of the more typical cases of the syndrome supports the view that it probably has a similar origin in most of these cases. An intra-partum hæmorrhage in the medulla appeared to be responsible for the unilateral 6th and 7th palsy in Bálint's case. I have referred to this case because it suggests that a similar pathology may be not infrequent in the apparently analogous group with unilateral facial palsy.

In the congenital eye muscle palsies absence or hypoplasia of the muscles concerned has frequently been observed at operation, but this may sometimes be secondary to nuclear aplasia. Destructive processes which involve the nuclei are sometimes the cause of the palsy as in Bálint's case. It is probable, however, that nuclear aplasia is the usual cause of bilateral congenital ocular palsies as in a case recently demonstrated by Phillips, Dirion and Graves (1932). In a 5-year-old child with an uncomplicated congenital bilateral abducens palsy they found an hypoplasia of the 6th pair of nuclei and nerves.

HISTORICAL REVIEW.

The writings of Moebius (1888, 1892) on the subject of "Infantiler Kernschwund" attracted considerable attention and excited a good deal of controversy. He regarded congenital cranial nerve palsies and those acquired in infancy and early childhood as fundamentally the same. He classified the forty-three cases of cranial nerve palsy in young children, which he reviewed, into six groups. Combined 6th and 7th nerve palsy comprised one of these groups. He found six examples in the literature—the first five of this series and the case described by Recken (1891) which was acquired. Moebius thought that 6th and 7th nerve palsies probably could not occur independently on account of the close relationship of their nuclei. In the absence of pathological evidence he thought the condition was most likely a degenerative one involving the nuclei of the affected nerves and that it was probably toxic in origin.

The views of Moebius were, for the most part, generally accepted, although several earlier writers were nearer the mark than he. Chisolm (1882) thought the lesion in the third case of this series was "a local aplasia of the grey matter in the medulla." Mauthner (1885) and Hirschberg (1887) thought that an aplasia of the cranial nerve nuclei accounted for these congenital palsies.

A change of opinion in favour of the aplastic conception followed the admirable review by Kunn (1895) of the subject of congenital ocular palsy in which he sharply differentiated between congenital and acquired types, and considered the former to be due to an aplasia of the corresponding nuclear cells. This hypothesis appeared to be confirmed by the pathological evidence of Heubner's typical case in 1900. The contradictory evidence presented by Rainy and Fowler's atypical case a few years later tended to confuse the issue, but the agenetic view continued to prevail pending further evidence. This was long denied, and not until 1931, when Spatz and Ullrich's case with multiple palsies was described, was confirmation of Heubner's findings realized.

Alajouanine, Huc and Gopcevitch (1930) thought they were the first to describe the association of club-foot with congenital facial diplegia, whereas nine of the cases of the present series previously recorded exhibited this anomaly.

Thomas (1898), Cabannes (1900) and Falloux (1909) reviewed the reported cases of congenital facial palsy, although they failed to include several of the hitherto published cases. More recently, brief and incomplete reviews were published by Fry and Kasak (1919), Kirby (1923) and Bonar and Owens (1929). Neurath (1907) and Zappert (1910) reviewed the available pathological evidence regarding congenital cranial nerve palsies in general, but the cases were few and varied and their conclusions were indefinite.

ÆTIOLOGICAL CONSIDERATIONS.

Hereditary factors.—Although males predominated, there was no significant difference in the sex incidence. Out of fifty-seven cases in which it was stated, thirty-four were males and twenty-three were females.

In four instances two or more members of a family were affected. Thomas's (1898) two cases were brothers, as were Köster's (1902), while a sibling of one of Cadwalader's (1922) cases was said to have been similarly affected. The three cases described by Beetz (1913) were siblings, and a fourth child of this ill-fated family, who died aged 15 months, was said to have had a mask-like face from birth and almost certainly suffered from the same congenital anomaly. There was a family history of congenital defects in Thomas's cases, also in Lennon's (1910) elder case and that of Fry and Kasak (1919). Though a family history of congenital deformities is not mentioned in any of the other cases it is probable that this may not always have been a matter of careful inquiry.

It is of interest to note that the siblings of Thomas, Köster and Cadwalader all belonged to the small group of uncomplicated facial diplegia. Consanguinity was a feature of the family described by Beetz in which there had been two instances of intermarriage in the previous three generations; the family lived in an isolated valley of the Black Forest where intermarriage is notoriously frequent. It is well to recall here that none of the three cases of this family was typically affected. It is evident that there is a definite tendency for the condition to show a familial incidence.

Ptosis is the commonest type of congenital eye muscle palsy: it usually has strong hereditary characters, the dominant being more frequent than the recessive type. Only occasionally can an hereditary factor be traced in the other types of congenital ocular palsy, such as those encountered in the syndrome under review. The hereditary type of ophthalmoplegia externa is rarely congenital: it usually exhibits dominant characters and makes its appearance in adolescence or later.

Toxic, vascular and mechanical theories.—Syphilis is no longer suspect in this condition; serological evidence was negative in each of the eight cases in which it was sought. Alcohol and other toxic agents were incriminated by some authors. Others thought that vascular defects might be the cause of the nuclear agenesis, but their views were purely hypothetical.

Mechanical influences of an extraneous nature were frequently exploited in this as in many other congenital anomalies. Some thought that pressure on the brain, arising from disturbances in its immediate surroundings, might explain the nervous phenomena.

Ullrich's hypothesis.—Ullrich (1930, 1936), who has been speculating on the ætiology of this syndrome for a number of years, believes that he has at last found a satisfactory explanation which accounts for its diverse features. His hypothesis is based on the embryological studies of Kristine Bonnevie (1934) who claims to have shown how somewhat similar anomalies arise in an experimental strain of mice. The mice belonged to the strain raised by Bagg and Little (1924, 1929) in the United States. They exhibited congenital deformities of the limbs and eyes in a high percentage of cases. These mutations were initiated by means of X-rays and their incidence was augmented by in-breeding through many generations: recessive genes were responsible for their passage.

In an endeavour to discover how the anomalies arise Bonnevie examined seven hundred live embryos of the Bagg-Little tribe at various stages of development. She claims to have shown that the fundamental error, which gives rise to all the anomalies, is an excessive production of cerebrospinal fluid by the newly-formed choroid plexuses of the developing brain. After the embryos attained a length of 7 mm. small subcuticular vesicles appeared on the back of the neck. In larger embryos increasing intra-vesicular tension appeared to be responsible for the dissipation of the contained fluid in the directions of least resistance, the elasticity of the cuticle being the displacing force and the least resistance being encountered on the most concave parts of the surface. The fluid finally came to rest in the orbital regions and at the ends of the limbs, but no permanent damage was done until it reached these situations. The pressure of the stationary fluid on the delicate underlying tissues usually caused capillary damage with intra-vesicular hæmorrhage and hæmatoma formation: thrombosis occurred in the subjacent vessels.

Comment.—Although no more than suggestive, Ullrich's hypothesis is the only one which would appear to have any justification. A critical examination of this new theory thus becomes necessary. No one has confirmed Bonnevie's observations. Plagens (1933) attempted to do so and failed, but he was not working with live embryos. However, Bonnevie's observations cannot be regarded with indifference, both because of their uniformity and of the high scientific reputation of the author. It is interesting to inquire how the cerebrospinal fluid could reach the subcutis to form the primary vesicle as postulated by Bonnevie. The fascinating experiments of Weed (1917) on the establishment of the cerebrospinal circulation show that an initial excess of cerebrospinal fluid would, in fact, be likely to take such a course.

Assuming that Bonnevie's explanation of the deformities in the Bagg-Little mice is the correct one, is there any justification for assuming that a similar process might account for the anomalies of the congenital syndrome under review? Ullrich finds no difficulty in applying it to these cases, but there are certain fallacies which appear to render his analogy untenable. He supposes that the primary vesicle overlying the roof of the 4th ventricle would press the roof against the floor of the ventricle and thus inhibit the development of the motor nuclei in that situation. This would, of course, be impossible owing to the greater intra-ventricular pressure which causes the fluid to filter through the temporary superior membranous area in the roof of the 4th ventricle. Further, if the pressure of the intra-ventricular fluid were sufficiently raised to damage the adjacent ectodermal tissue it would be most unlikely to exert a selective effect on certain nuclei to the exclusion of others.

For the purpose of testing Ullrich's hypothesis I intended to examine the brain-stems of a series of Bagg-Little mice for nuclear defects, but I was unable to procure them. If Ullrich's views are correct one would have expected to find evidence of hypoplastic motor nuclei.

It would appear then, that although such a process as described by Bonnevie might conceivably account for the limb and pectoralis muscle defects in the patients of this syndrome, it could not possibly be the cause of the nuclear defects in the brain. As all the anomalies are most likely to be due to a common factor one must conclude that Ullrich's hypothesis is untenable and that the ætiology of this congenital syndrome is still obscure. Bonnevie, Plagens and others agree that thrombosis, however it may arise, is a potent cause of congenital defects in experimental animals. Perhaps it accounts not only for the deformities of this syndrome, but also for the cerebral hypoplasia.

SUMMARY.

A review of the literature on the subject of congenital facial diplegia has been undertaken. A well-defined clinical picture has emerged as a result of this study.

A typical case has been described in detail, the patient being a girl aged 3 years.

The facial diplegia was usually accompanied by other cranial nerve palsies, while malformations of the limbs were frequently encountered The incidence of the principal anomalies was as follows:—

Facial diplegia	61	cases
Abducens palsy	45	,,
Ophthalmoplegia externa	15	,,
Ptosis	6	,,
Lingual palsy	18	,,
Mental defect	6	,,
Club-foot	19	,,
Brachial malformation	13	,,
Pectoralis muscle defect	8	,,

The facial diplegia was complete in one-third of the cases. When the palsy was incomplete, the distribution was characteristic, the peri-oral muscles being least affected and usually the only ones capable of any movement. No other type of facial palsy has such a distribution.

Pathological data are available in only three cases. The basis of the cranial nerve palsies was an aplasia or hypoplasia of the relevant nuclei and the nerves and muscles connected therewith.

The ætiology of congenital facial diplegia is obscure. The principal theories regarding it have been discussed.

It is a pleasure to acknowledge my indebtedness to Professor Charles McNeil for the interest he has shown in this work.

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DYNAMICS OF HOMONYMOUS HEMIANOPIAS AND PRESERVATION OF CENTRAL VISION.

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An analysis of homonymous hemianopias associated with tumours of the brain reveals a considerable percentage of cases in which there is preservation of the central field, the so-called "macula-sparing" hemianopias. In a study of 600 cases of brain tumours, complete or "macula-splitting" hemianopias were uncommon in tumours of the suprageniculate pathways.

In our series of cases, it was found that the periphery of the field of vision was affected first, the hemianopias progressing towards the centre. In the cases of brain tumour and hemianopia reported in the literature, the earliest defects in the homonymous fields were invariably in the periphery (Cushing, 1921; Globus and Silverstone, 1935; Bender and Strauss, 1937). Associated with these changes in panoramic vision for black and white were disturbances in colour vision. The hemianopias for colour invariably preceded those for black and white, and again the disturbances progressed from the periphery to the macula. It seemed that the various field defects recorded in our series of cases were stages in the development of the hemianopia, and in all these instances, vision in the macular region was last to disappear.

The zone of preserved central vision in the cases studied ranged in extent from 5° to 30° from the fixation point depending on the degree of acuity and the extent of the hemianopia.[1] This preservation of central or "macular" vision occurred irrespective of which part of the optic radiation was involved by the tumour. Moreover, it was noted that the character and the development of the hemianopia were similar in neoplasms of the temporal and occipital lobes. In almost all instances, the homonymous field of vision contracted from the periphery centrally.

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[1] The actual extent of the area of macular vision is from 2° to 10° around the fixation point.

I.—Stages of Hemianopias.

The following case reports illustrate various stages in the development of homonymous hemianopias. There were many such examples but space does not permit their full description.

Case I.—A 42-year-old male was first admitted to the hospital in July, 1936, with a history of severe headaches which began suddenly while straining at stool. The onset was accompanied by vertigo and vomiting. Previously the patient had been subject to milder headaches for four months. Examination on admission revealed nuchal rigidity and bilateral Kernig sign. There was marked mental confusion and aphasic symptoms. Visual field defects were noted but could not be plotted. Lumbar puncture yielded deeply bloodstained fluid. The patient improved and was discharged with a diagnosis of subarachnoid hæmorrhage.

In December, 1936, he had a generalized convulsion and persistent headache, drowsiness and mental symptoms. Examination on the second admission revealed an incomplete right homonymous hemianopia (fig. 1) and symptoms of mixed aphasia. An encephalogram revealed internal hydrocephalus. The symptoms persisted. A craniotomy was performed and a cyst was discovered in the left temporo-parietal region. Needle aspiration yielded 2 c.c. of yellow fluid. After operation the condition of the patient was unchanged except for increased aphasic difficulties.

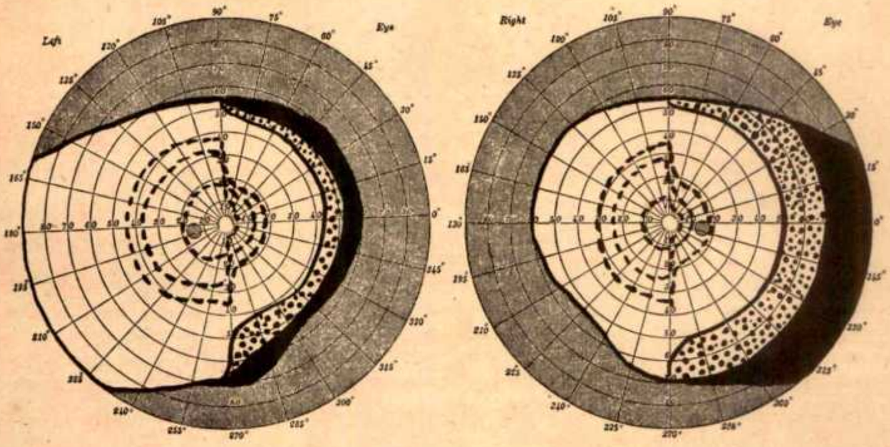

FIG. 1.—Early right homonymous hemianopia. The solid area represents an absolute scotoma for 10 mm. test object. The stippled area is a relative scotoma for 4 mm. test object. Dashes indicate colour vision as determined by 10, 4 and 2 mm. test objects.

Comment.—This is an example of an early peripheral defect in the homonymous fields of vision.

Case 2.—A 47-year-old housewife entered the hospital because of frontal headache, blurred vision, and speech difficulty of four weeks' duration.

Examination disclosed a slight right facial weakness, anosmia and blurring of the optic discs. Perimetric field examinations showed an incomplete right homonymous hemianopia. When she was asked to bisect horizontal lines she invariably

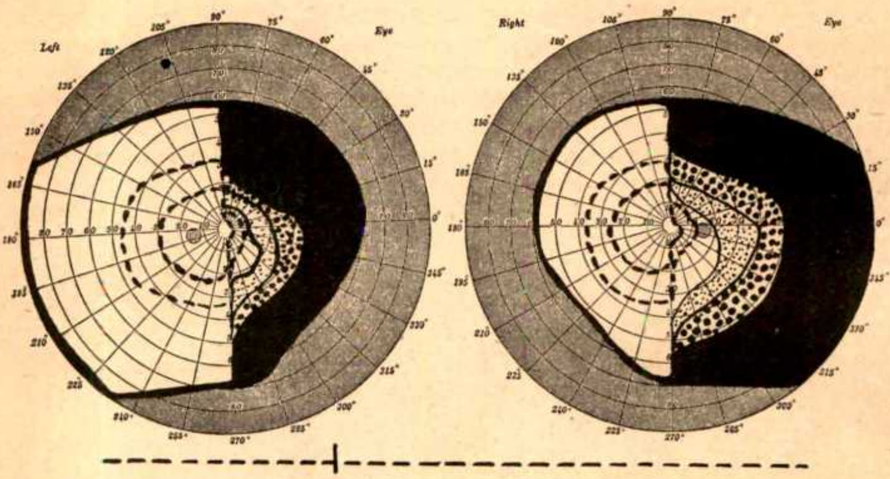

FIG. 2.—A more advanced stage of a right homonymous hemianopia. Such field defects were not uncommon. The hemianopia is incongruent and greater in the upper quadrant. Solid black represents outer border for 10 mm.; heavy dots is border for 4 mm. and light dots is border for 2 mm. test object. The dash lines are colour fields for 10 and 4 mm. test objects. In the stippled area the patient recognizes motion of a 10 mm. object but can perceive neither colour nor form. The horizontal dash line below the perimetric fields represents a red coloured line which the patient was asked to bisect. The patient divided the line to the left of the true midpoint, but soon realized her error.

divided the line to the left of the true midpoint. Once she realized her error and remarked that she did not notice the right side (fig. 2).

A ventriculogram confirmed the clinical diagnosis of left temporal lobe tumour. At operation a neoplasm was located deep in the left temporal lobe.

Comment.—This is a more advanced stage of a homonymous hemianopia. An interesting feature was the patient's division of the horizontal line to the left of the actual midpoint. Apparently the patient formed a new macula. The formation of a pseudo-fovea is not uncommon in individuals with homonymous hemianopia.

Case 3.—A 17-year-old boy was admitted with a history of illness of five weeks' duration. The symptoms included weakness of the left upper and lower extremities, difficulty in swallowing with nasal regurgitation and spells of dizziness associated with unpleasant olfactory sensations. Examination revealed incomplete left homonymous hemianopia (fig. 3). An exploratory craniotomy was performed and tumour tissue removed from the region of the right posterior temporal lobe. The extent of the tumour could not be determined. The post-operative recovery was uneventful. Histological studies of the tumour revealed a neurospongioblastoma.

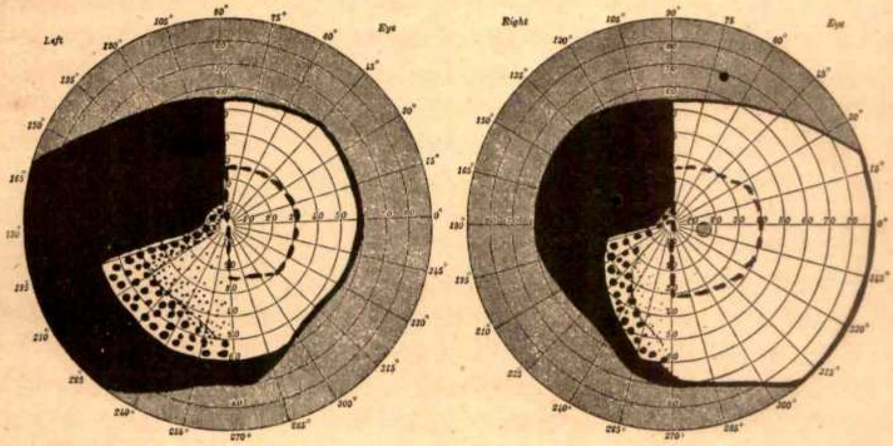

FIG. 3.—Incomplete left homonymous hemianopia with the defect, except for central vision, being greatest in the upper quadrants. The solid black is an absolute scotoma. The heavy dots indicate recognition of motion by a 10 mm. object. The small dots represent the same function for a 4 mm. object. More centrally, objects appeared clearer. The dash lines represent the visual field determined by a 4 mm. green test object, showing a macula-splitting hemianopia for colour.

Comment.—In the inferior left homonymous quadrants the vision was contracted from the periphery centrally and the acuity was very much reduced. The defect was greatest in the periphery and least in the centre. The colour hemianopia was complete, there being no sparing of the macular region. Apparently the fibres conducting light impulses from the right homonymous upper retinæ were not entirely destroyed although definitely damaged. The function of the rest of the right optic radiation was completely impaired. This is an example of a more advanced stage of homonymous hemianopia. If the disease process were permitted to continue without operative interference the hemianopia would become complete. The defects in the fields of vision show incongruity; the nasal half was more extensively affected than the temporal. This was a common finding.

The foregoing data show that the development of a hemianopia is progressive in character. Examination limited to a single perimetric determination discloses field defects which are only phases in the development of the hemianopia. When subsequent field examinations are made at later stages of the process, the extent of visual impairment is often found to have increased. This was demonstrated in several of a series of cases reported by Bender and Strauss (1936). In the early stages, there may be a peripheral temporal crescentic scotoma ; later, a defect may be discovered in the homonymous peripheral field ; eventually, when the homonymous paracentral zone becomes affected, the central region is still relatively uninvolved. Careful examination of this supposedly spared "macular" region with coloured and small test objects may disclose a colour defect which extends up to the fixation point. Such studies tend to reveal that the hemianopia for colour precedes that for form.

II.—THE LOSS OF COLOUR VISION PRECEDING LOSS OF FORM VISION.

There has been frequent confirmation of the fact that in lesions of the suprageniculate pathways, colour vision is usually more severely impaired than is perception of black and white (Magitot and Hartmann, 1926 ; Brouwer, 1936). It is not unusual to find a quadrantic defect for form associated with a complete homonymous hemianopia for colour. Our own observations also show that in the progressive development of hemianopia, colour vision is affected first and that at a time when testing with form objects shows "macula-sparing," tests with red, blue or green objects will already show a complete macula-splitting hemianopia. In these cases the central area of vision is only relatively preserved and there are definite indications that macular fibres are involved.

The conduction of colour vision has been regarded by some authors as separate from the conduction of black-white sensation. In support of this supposition, cases of "pure" colour hemianopia have been cited. Wechsler (1933) gives an excellent review of the literature upon the subject of dissociation of colour and form vision. In two cases in which post-mortem examination was performed by Lenz (1921), lesions were found in the occipital radiation. Brouwer (1936) points out that the assumption of separate conduction of colour vision is unnecessary and it is probable that in most cases of colour hemianopia, careful examination will reveal that black-white vision is not completely unaffected. We followed his suggestion but detailed perimetric testing in patients with colour hemianopia showed no change in black and white perception. The following are examples.

Case 4.—The patient was a 23-year-old female who was admitted with a history of headache, nausea and convulsions of four weeks' duration. She also had visual hallucinations of formed images and figures. A physician detected a suggested left homonymous hemianopia on one occasion. Lumbar puncture showed 200 red blood-cells in the spinal fluid. Neurological examination revealed bilateral papillœdema, symptoms of meningeal involvement and a left homonymous visual defect for colour but not for form. The diagnosis was subarachnoid hæmorrhage.

In the hospital, the condition of the patient improved rapidly. Repeated visual field examinations showed gradual improvement in the perception of colour. Perimetry executed three years later showed an incomplete left homonymous hemianopia for colour which was most evident for 1 mm. green test object. There was absolutely no disturbance in the peripheral fields of vision for black and white (fig. 4).

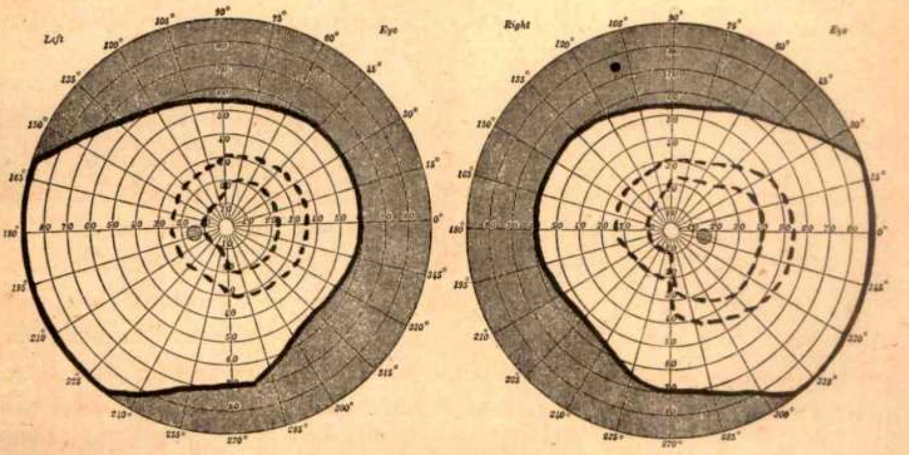

FIG. 4.—Left incomplete homonymous hemianopia for colour. Dash lines represent the fields as established with 10 and 4 mm. coloured test objects. The outer form field was determined with 10, 4 and 2 mm. objects. This revealed no defects.

Comment.—These observations are at variance with Brouwer's hypothesis. It is possible that some of the fibres scattered throughout the optic radiation were damaged at a focal point and this resulted in a partial reduction in the visual acuity which became manifest in the form of a hemianopia for colour.

Case 5.—A 36-year-old female was admitted following an attack in which she lost consciousness but was not convulsed. There was a history of a craniotomy at another hospital six months previously. At that time, a large tumour of the gasserian ganglion was reported to have been completely removed. Before the operation there had been weakness of the left extremities which had partially recovered their power since the removal of the tumour. After the operation she suffered from attacks of depression, absent-mindedness and difficulty in spelling and speech. Examination at the time of admission showed a right homonymous visual field defect for colour (fig. 5). Except in the "macular area" she was unable to recognize colour, form, or objects in the right homonymous field of vision. She was, however, able to appreciate movement even in the most extreme periphery of the defective right field of vision.

No other noteworthy symptoms developed and the patient was discharged. She was examined periodically during this time. Repeated perimetry disclosed loss of recognition of form and colour but retention of appreciation of movement in the right homonymous fields.

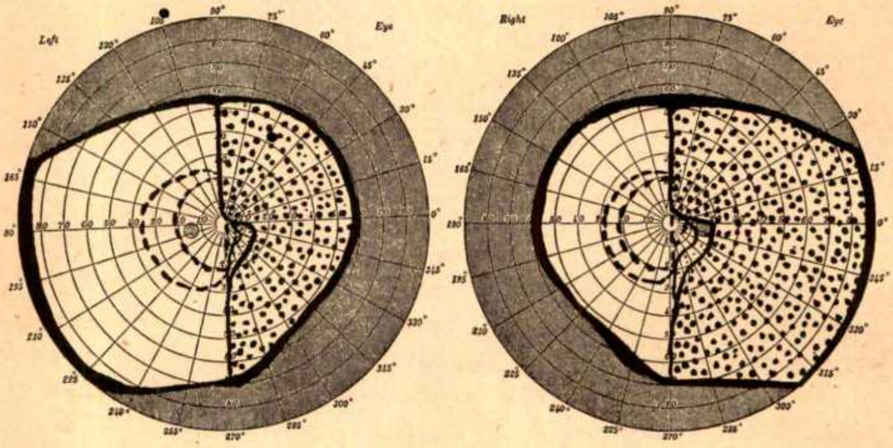

FIG. 5.—Right homonymous hemianopia for colour and form. Heavy dots represent areas in which only motion could be perceived. The dash lines are outlines of colour fields for 4 and 2 mm. objects and show a macula-splitting hemianopia. There is no absolute scotoma in the peripheral fields.

Comment.—This is an example of homonymous hemianopia for recognition of form and colour and preservation of recognition of movement even at the most extreme periphery of the field of vision. We lack an explanation for this observation even though there may be many hypotheses.

Whichever hypothesis be correct, it appears that the early loss of colour vision is a sign of impairment of the finer functions of the optic pathways. Since visual acuity as well as colour vision is progressively impaired as the optic radiation is gradually involved, it is evident that the peripheral defects are only part of a greater disturbance in vision. If the anatomical facts be considered, it is clear that where an infiltrating lesion, such as a tumour, affects the optic radiation by œdema, the function of the entire radiation, including the peripheral and central fibres, will be disturbed. Since the peripheral fibres are fewer in number and occupy a smaller area than the central fibres, and inasmuch as they represent areas of less visual acuity,[1] their functional impairment is more readily followed by visual field defects. Consequently the earliest defect in the field of vision makes its appearance in the periphery. In the more central parts of the field of vision, the earliest sign of partial impairment of the functions of the central optic fibres is found to be the loss of acuity for colour vision. Only after the functional impairment has become severe is the acuity for black-white perception affected. This, of course, depends on the number of conducting fibres destroyed.

III.—Macular Vision and Occipital Lobe Tumours.

The foregoing data show that central vision for form is often preserved in homonymous hemianopias. The occurrence of homonymous hemianopias with "sparing of macular vision," in these cases, has led some observers to postulate bilateral cortical representation of each macula. Foerster (1929) and Penfield, Evans and MacMillan (1935) believed that sparing of macular vision after removal of the occipital lobe afforded evidence of bilateral representation of the macula. These observations were used to support the theory that macular fibres decussate through the corpus callosum to reach the opposite occipital lobe. Pfeiffer (1925) found such a decussation, but Putnam (1926) was unable to confirm this finding.

The preservation of central vision in a homonymous hemianopia resulting from an occipital lobe tumour may be explained by any one of several theories. A hypothesis of bilateral cortical representation has many adherents but at variance with it are certain facts: (1) Numerous anatomical studies made on experimental animals showed that the two suprageniculate pathways are not connected through the corpus callosum or by other association fibres (Poliak, 1932). (2) Clinico-pathological observations revealed that lesions of one occipital pole produced contralateral homonymous hemianopic central field defects (Holmes and Lister, 1916; Holmes, 1918; Wilbrand, 1907), and that tumours of the occipital lobe may produce macula-splitting hemianopias. The available data seem to indicate that the homonymous half-maculæ are represented in one occipital lobe. Support for the theory of bicortical macular representation, however, is found in clinical observations of preserved central vision in patients with occipital lobe tumours (Allen, 1930; Horrax and Putnam, 1932). Thus, the tumours in some of our cases invaded the cortical macula in the occipital lobe, leaving only a small portion, the most anterior part, intact (Case 6). In other instances, the tumour did not involve the calcarine cortex but was localized on the lateral aspect of the occipital lobe (Case 7).

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[1] Functionally, it has been shown by Traquair (1938) that the acuity in a highly illuminated field of vision is greatest in the centre and decreases toward the periphery. The threshold visual stimulus for the central area is less than for the peripheral field of vision. This is also true for colour vision.

Case 6.—A 32-year-old male was admitted to the hospital with a history of generalized convulsive seizures during the past eight years. These attacks had become increasingly frequent, and recently headaches and impairment of memory had developed. The examination revealed signs of a lesion in the left cerebral hemisphere, including a right homonymous hemianopia with sparing of central vision. A craniotomy was performed and some calcified tumour tissue was removed from the occipital pole. Histological study of the excised brain tissue suggested a vascular anomaly. Perimetry now disclosed the right homonymous hemianopia to be more complete. There was an area of apparent central vision remaining, being 5° to 10° from the fixation point. Stereocampimetry showed an area of preserved central vision (fig. 6).

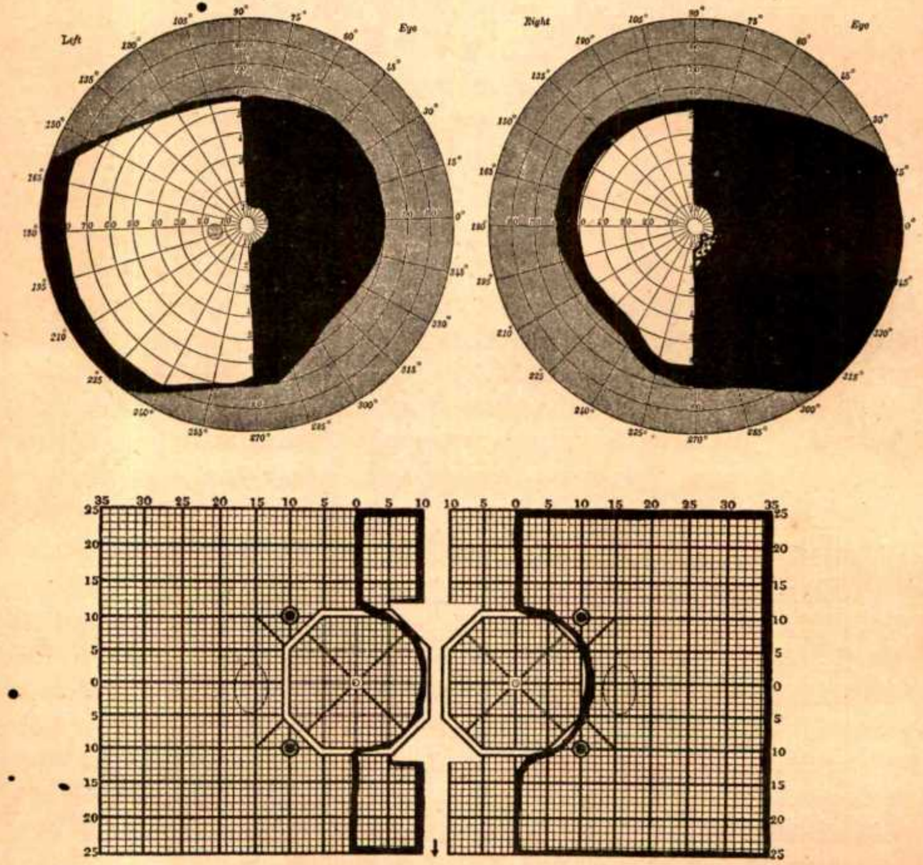

FIG. 6.—Right homonymous hemianopia with preservation of central vision. The lower chart is plotted from a stereocampimeter.

The convulsive seizures continued and a second operation after a lapse of eight months revealed cystic changes in the occipital lobe, which was amputated behind the temporo-parietal junction. Following the second operation, examination of the fields of vision revealed a right homonymous hemianopia which seemed to spare the macula from 2° to 5°. On the tangent screen test and on stereocampimetry the zone of apparently preserved vision was not circular in its outline. The inner border of the hemianopia was an irregular wavy vertical meridian (fig. 7). This was due to formation of a new macula.

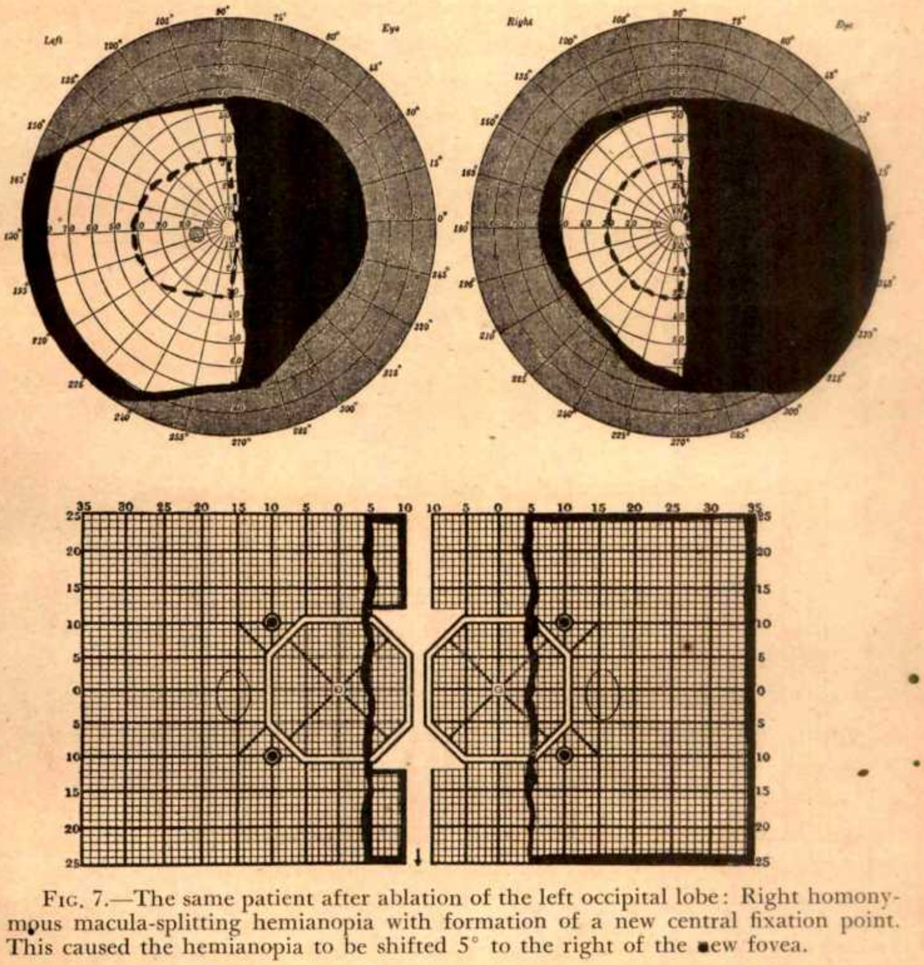

Fig. 7.—The same patient after ablation of the left occipital lobe: Right homonymous macula-splitting hemianopia with formation of a new central fixation point. This caused the hemianopia to be shifted 5° to the right of the new fovea.

Four years later a perimetric examination disclosed a right homonymous hemianopia and the formation of a new macula. The macula-splitting hemianopia was 3° to 5° to the right of the point which the patient was asked to fix during perimetry.

Comment.—This is an example in which the lesion involved the cortical macula and yet the macular field of vision seemed to be preserved. Amputation of the occipital pole did not abolish macular vision. Only after the entire occipital lobe was excised did the hemianopia split the macula, and this appeared in conjunction with a new or "pseudo-macula." The preservation of central vision in this case may be explained by various hypotheses, such as a psychological reorganization of visual function in the remaining cortex, a diffuse representation of the macula, or by the formation of a new functional macula. The theory of bilateral representation of the cortical macula is not supported by this case because amputation of the entire occipital lobe resulted in a shifted macula-splitting hemianopia. The area of preserved vision was the result of a shifting of the macula—the inner border of the hemianopia being a straight line and not a semicircle.

Case 7.—The patient was a 20-year-old male who had been suffering from severe frontal headaches for three years. Two years before admission he had been fitted with glasses because of visual difficulties, but was not benefited. The physical examination in the hospital revealed a bilateral low grade papillœdema and an incomplete left homonymous hemianopia. A ventriculogram was performed and a large cyst in the right parieto-occipital region was outlined. At

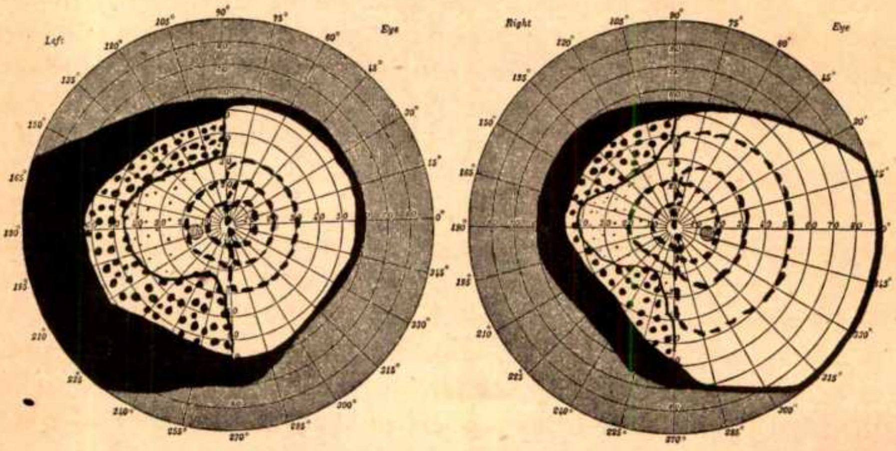

FIG. 8.—Incomplete left homonymous hemianopia. The solid black indicates an absolute scotoma. Heavy dots represent the area visualised by a 4 mm. test object. Small dots represent the zone visualized by a 1 mm. test object. Note the sector defects as outlined by the heavy dots. Dash lines represent borders for colour vision, concentrically 10, 4 and 1 mm. test objects. There is a macula-splitting hemianopia for green 1 mm. object.

operation, a hæmangioma was removed from the lateral surface of the right occipital and parietal lobes. After operation, a left homonymous hemianopia was found. The patient recovered without further complications and has remained well.

Perimetric examination performed six years later showed an incomplete left homonymous hemianopia for form with tendency to sector defects (fig. 8). With varied sized test objects the defect was made more apparent. The colour hemianopia was even more pronounced. There was only a relative sparing of vision in the central area.

Comment.—The hemianopia observed in this patient who had a lesion of the optic radiation in the occipital lobe is not different from the type of hemianopia seen in patients with lesion of the radiation in the temporal lobe. The field defect is most pronounced in the periphery but the central area is relatively equally affected. An interesting finding was the tendency to the formation of sector scotomata in the upper and lower fields of vision. This was particularly apparent with smaller sized test objects.

Some observers maintain that macular vision is widely represented in the occipital cortex (Fox and German, 1936). The anatomic evidence of Poliak (1932), however, favours the principle of a spatially organized projection system in the visual pathways. According to his studies of myelin sheath degeneration of the optic radiation, a wide cortical representation of the macula does not exist. Poliak admits that he did not examine the axis cylinders or the numerous fibre connections which exist in the cortex and subcortex. A consideration of the latter reveals that after the macular fibres reach the occipital lobe, they aborize and make wide and intricate associations with different parts of the cortex. It is well known that the end ramifications of nerve fibres partially overlap. This principle of overlapping of nerve paths has been found by Lorente de No (1934) to be a " general law of structure of the nervous system." In his discussion of point-to-point relationship in the visual system, Lorente de No stated that " each point of the retina is projected into a larger area of the cortex because the arborizations, protoplasmic as well as the axonal ones, are extensive, and therefore impulses set in any point of the retina may be transmitted to a larger area of the cerebral cortex. However, assuming that the neuron is a summation apparatus which reaches threshold excitation only when a certain number of its synapses are active, it becomes evident that physiologically the projection of the retina on the cerebral cortex may be point-like." The visual cortex may be so organized that each integral part receives impulses from all parts of the retina but in a differential manner. Thus there may well be a wide representation of the macula in the occipital cortex in which the predominant number of impulses of macular origin reach the most posterior part of the striate area while the remainder enter other parts of the cortex. At the same time, fibres from the peripheral retina are predominantly represented in the anterior part of the area striata (Spence and Fulton, 1936) and a much smaller number connect with the occipital pole or cortical macula. Theoretically, destruction of the most posterior striate cortex alone should produce a corresponding homonymous hemianopic macular scotoma. If, however, the adjacent subcortical association or optic radiation fibres going to other parts of the cortex are involved in addition, then the resultant defects would be more widespread.[1] A reduction in the visual function of the entire homonymous field would follow. Since the acuity of the peripheral field of vision is low, any slight impairment of function representing the periphery would produce corresponding scotoma, which, in association with the homonymous central field defect, should result in a macula-splitting homonymous hemianopia. This, however, did not occur; some macular vision remained. If any fibres reach any part of the remaining visual cortex, there will be some preservation of central vision. Each integral part of the visual cortex may be so organized that impulses reach the cortex from all parts of the retina. Here they are integrated in patterns in which central vision assumes the highest acuity and peripheral vision the lowest. This, of course, would result in a markedly contracted homonymous field, thus giving a picture of homonymous hemianopia with relative sparing of the macula.

These hypotheses lead us to the theory of formation of a new "functional macula" postulated by Fuchs (1920) and supported by Goldstein (1925). This theory postulated a redistribution of energy in the intact portions of the visual field about a new functional centre of brightest vision, the "pseudo-fovea." This functional entity does not coincide, as in the normal field, with the fixation point but shows a displacement towards the side of preserved vision. The position of this "pseudo-fovea," accordingly, would correspond with an eccentric spot of the still functioning part of the retina (Kanzer and Bender, 1939). With lesions of the occipital lobe the patient may develop a new fixation point.[1] Perimetric examination in these cases will reveal an area of preserved vision on the hemianopic side of the fixation point. Careful examination, however, will show that the zone of preserved vision is not circular but linear in the vertical meridian. This is due to the displacement of the macula-splitting hemianopia to one side by the formation of a new central fixation point. Such a shift is of significance in estimating the extent of the "macula-sparing" and in determining the peripheral boundaries of the visual field. This factor is neglected in performing the usual tests for the peripheral field of vision, which require an enforced static position of the eye that does not permit the manifestation of important visual psychomotor disturbances resulting from lesions in the parieto-occipital region (Fox and Holmes, 1926; Hoff and Pötzl, 1933). Nevertheless, the psychomotor adaptation of the eye necessarily assumes an important rôle in the total visual process, determining not only the direction of attention but the form of perceived objects (Kanzer and Bender, 1939). Such considerations emphasize the necessity of regarding vision as a total function rather than as a strictly determined correlate of anatomic pathways.

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[1] It must be remembered that a tumour of the occipital lobe which causes symptoms involves not only the cortex but the subcortex and optic radiation as well. The physiological changes produced in these instances cannot be the same as in lesions of the cortex alone. Pure cortical lesions are extremely rare. The homonymous scotomata that result from lesions in the calcarine area may be attributed not only to the involvement of the cortex but to the implication of the immediate subcortical association fibres as well.

DISCUSSION.

Presumably, in our cases with tumour involving the occipital pole ("cortical macula"), the preservation of central vision is due to a shifting of function to another part of the calcarine cortex (the most anterior part) or to a widespread representation of the macula in the cortex, or both. We do not believe that the cortical macula is bilaterally represented. In cases of tumour involving the optic radiation in the temporal lobe, other factors must be considered. The dynamics of the hemianopias in these cases may be accounted for by the anatomical characteristics of the geniculo-calcarine pathway and by the progressive nature of the disease process which occurs with brain tumours.

The internal structure of the visual pathway has been ascertained by the method of myelin sheath degeneration (*see* fig. 9). Brouwer and Zeeman (1926), Putnam and Putnam (1926) made small lesions in the retina of monkeys and rabbits and traced the degeneration along the infrageniculate course. Similarly Poliak (1932) studied the degeneration between the lateral geniculate body and the occipital lobe cortex. Each investigator found every point of the retina to be projected throughout the central visual system in a definite order. In a general way the arrangement of the dorsal, ventral, temporal and nasal fibres of the retina maintained their respective positions throughout the entire retino-geniculo-calcarine pathway. In the

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[1] Fixation is brought about by directing the eye so that the object is in line with the visual axis, its image falling upon the fovea. During fixation the eye is not absolutely steady, but makes constant slight excursion, so that the fovea traverses the different parts of the objects regarded and produces a synthetic picture. If there is a disturbance in central vision, such as occurs with macula-splitting hemianopia, the retina of each eye will move into such a position as to obtain the best fixation possible, thus forming a new fovea.

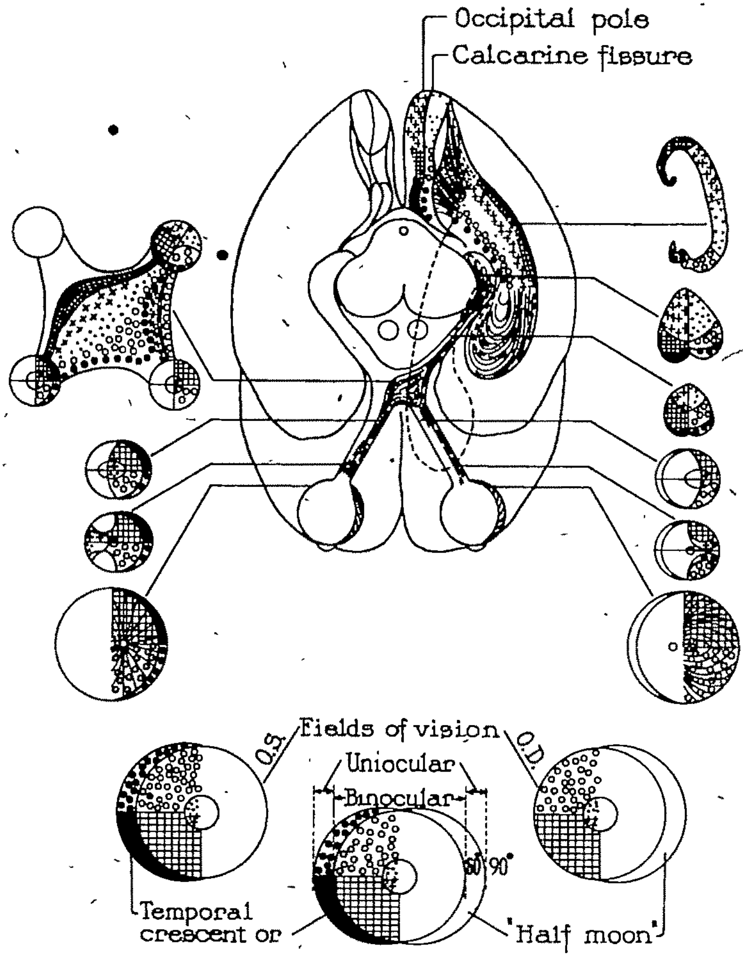

Fig. 9.—Schema illustrating the probable course of the afferent visual pathways at different levels of the nervous system and their projected visual fields. Reconstructed and modified from the works of Brouwer and Zeeman (1926), Wilbrand (1926) and Poliak (1932).

optic radiation the fibres arrange themselves in a vertical plane (*see* fig. 9). The macular fibres are in the middle of the geniculo-calcarine path ; the fibres from the upper retina (illustrated by crosses in fig. 9) traverse the upper half, and the fibres from the lower retina (represented by small dots) course through the lower half of the vertical rim of the optic radiation. The fibres peripheral to the upper macular region (indicated by cross-hatched lines) are placed more superiorly, and the fibres peripheral to the lower macular region (illustrated by circles in the figure) are located more inferiorly in the radiation. The most peripheral fibres, derived from the upper and lower halves of temporal crescents and representing uniocular vision, are on the extreme upper (solid black) and lower (heavy dots in figure) edges of the vertical rim respectively. The number of optic fibres representing different parts of the field of vision and the area projected by them in the radiation decreases from the centre toward the periphery. The macular fibres are largest in number and cover a greater area than the peripheral fibres. The "crescent" fibres are fewest in number and cover the least area. The change is gradual, there being no sharp demarcation between two closely adjacent points in the field of vision.

The disturbances produced by tumours in the temporal or occipital lobes are rarely limited to the confines of the tumour itself. In cases of tumour of the brain implicating the optic radiation, the function of the entire geniculo-calcarine pathway would be impaired by œdema surrounding the neoplasm. In view of the anatomical facts cited, the earliest disturbances may be expected in the field of vision subserved by fibres which conduct the lowest visual acuity or where the fibres are fewest in number and occupy the smallest area. Actually, the regions subserved by the peripheral temporal fibres are involved first (Bender and Strauss, 1936) ; these fibres are fewer in number and cover less area than the fibres representing the central fields. As the pathological processes progress, an increasing number of fibres are involved and a corresponding defect from the periphery to the centre becomes manifest. Thus a pathological link between the anatomical and clinical finding is provided.

Efforts made with several patients to elicit minute discrete scotomata in the area of preserved central vision were unsuccessful: there were no such scotomata. Such an absence of scotomata with lesions of a spatially organized optic radiation suggests that this structure operates as an entity rather than as a conglomeration of separate visual units. Inasmuch as the function of the entire radiation is impaired, all the individual components are necessarily affected.

In conclusion, it should be emphasized that the studies on homonymous hemianopias associated with tumours of the brain permit the progressive nature of the visual disturbance to be followed. In this way, certain factors emerge which cannot be determined when the observations are limited to cases in which lesions have occurred suddenly, such as trauma and cerebro-vascular accidents. In a gunshot wound of the brain or in an occlusion of one of the cerebral vessels, the resulting homonymous hemianopia appears immediately and as time goes on there is regression of the hemianopia. We have followed patients with homonymous field defects associated with thrombosis of middle cerebral artery. When improvement occurred, central vision returned first and then enlarged in area peripherally. In tumours of the brain, however, the reverse is true. The homonymous hemianopia sets in gradually, unless, of course, there is an accompanying occlusion of a vessel. The field defect begins in the periphery and advances centrally. The rate of progression depends on the rate of the tumour growth and of alteration in the surrounding tissues. Regression is rare, because of the progressive nature of the neoplasm.

In inflammatory lesions, that is, non-suppurative encephalitis, we may follow the complete cycle of development and regression of a homonymous hemianopia (Bender and Strauss, 1937). In these instances the lesion develops and regresses slowly and thus allows of frequent examination of the fields of vision.

SUMMARY.

Observations on cases of progressive hemianopia associated with tumours of the brain indicate that there is a concomitant relationship between visual acuity, colour vision and peripheral defects in the visual field. So-called " macula-sparing " in cases of homonymous hemianopia is found to be a stage in the development of a complete hemianopia, the defects beginning in the periphery of the field and gradually spreading toward the centre. Careful examination of the " preserved " field of vision will often disclose diminished visual acuity and impairment of colour vision, indicating an early disturbance in the function of the visual pathways. These findings suggest a functional integrity of the optic radiation, a hypothesis which finds further support in the fact that examination fails to reveal minute scotomata in the areas of preserved vision such as should be found with a diffusely involved organization of discrete optic units. This conception of functional unity of the optic radiation is useful in explaining the sparing of central vision irrespective of the localization of the lesion within the radiation and provides an alternative, in many cases, to a hypothesis of bilateral representation of the macula. Criteria for judging

the extent of macula-sparing are discussed and the observation made that instances of complete loss of macular vision resulting from brain tumour are very rare.

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BLOOD CHANGES IN DYSTROPHIA MYOTONICA

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Although there has been a considerable amount of research into creatinine and creatine changes in blood and muscle in cases of dystrophia myotonica very little attention has been directed to changes in potassium in the blood or muscle. (Recently Leulier and Pommé (1934, 1935) and Cumings (1939*b*) have estimated the potassium content of muscles from patients with myotonia. The last author showed that muscles from affected areas contained a lower potassium content than normal muscles. It seemed that certain investigations into the serum potassium might yield results of value. Allott and McArdle (1938) have shown that large doses of glucose and injection of insulin reduced the serum potassium and at the same time produced paralysis in patients with familial periodic paralysis. Similar procedures to those used by these authors were undertaken in two patients with myotonia. Potassium was estimated in the serum (Cumings, 1939*a*), and at the same time some other substances were also estimated. These were calcium, inorganic phosphorus, chlorides, magnesium, urea and sugar (using methods as used in a previous investigation (Cumings, 1938)). Blood was taken before and after the administration of glucose and insulin.

The results obtained showed no significant changes between the two blood samples in either patient. The serum potassium contents were 22·97 mg. per cent. and 16·24 mg. per cent. before, and 19·37 mg. per cent. and 17·63 mg. per cent. after the experiments respectively. The sugar level fell slightly in both patients, and there was a slight rise (less than 10 per cent.) in the chloride level between the two samples of blood in both patients. The other constituents examined did not alter at all.

Exercise Experiments.

The effect of exercise on the serum potassium was then studied. The exercises consisted of fairly rapid walking, together with simple arm exercises for a period of half an hour, and these were conducted as far as possible at the same time of day in every case. Blood was taken before and after the period of exercise.

The patients examined consisted of eleven cases of myotonia, two of myasthenia gravis, two with loss of muscular power comparable to the loss found in the patients with myotonia, and two perfectly normal male subjects.

Plasma chlorides were determined on the first three cases of myotonia and on the two cases with muscular weakness, in case any alteration of total blood composition took place which could be detected by this means. There was no alteration at all in the chloride level before and after exercise.

RESULTS.

The two normal subjects, the two patients with myasthenia gravis and the two patients with loss of muscular power showed no significant alteration in the serum potassium levels before and after exercise. The two patients with myasthenia gravis had slightly low potassium contents. They were 15·08 mg. per cent. and 18·27 mg. per cent. and these fell to 14·15 mg. per cent. and 16·53 mg. per cent. respectively.

The eleven cases of myotonia could be divided into two groups on clinical examination. The first group consisted of four patients who showed marked myotonia with no wasting or only wasting of a slight degree. The second group of seven patients showed very slight myotonia with definite wasting. The presence of myotonia and of muscular atrophy in the face and neck was disregarded as the exercises only involved muscles of the extremities.

Table I shows the results in the first group together with indications as to the degree of myotonia and wasting.

TABLE I.

Patient	Degree of myotonia	Degree of wasting	Potassium before exercise in mg. %	Potassium after exercise in mg. %
Mr. B.	++	—	15·78	9·51
Mr. S.	++	—	24·84	17·01
Mrs. V.	++	±	25·2	14·4
Miss B.	+	±	24·01	19·14

Table II gives the results found in the second group.

TABLE II.

Patient	Degree of myotonia	Degree of wasting	Potassium before exercise in mg. %	Potassium after exercise in mg. %
Miss D. . ..	±	+	14·15	15·54
Mr. D. ...	±	±	15·78	16·94
Mr. R. B. ...	±	±	13·22	13·92
Mr. H.	±	±	17·92	17·4
Mr. J. L. McD. ...	+	++	21·23	21·58
Mr. J. McD. ...	±	+	15·9	24·1
Mr. E. McD. ...	±	±	18·62	18·27

It is seen that in all four patients in the first group there is a very definite fall in the serum potassium after exercise, although this is less marked in the last case, which showed the least amount of myotonia in this group. Three of these patients had normal resting potassium levels. Patients in the second group, however, show no alteration in the potassium level after exercise, but many of them show a low resting level. All except one (Mr. D.) in this second group are cases of long duration of the disease.

Fenn and Cobb (1936) have shown that during muscular contraction there is a loss of potassium from muscles of animals. The two normal subjects showed no appreciable alteration in the potassium level after exercise, but it seems hardly likely that the changes shown by Fenn and Cobb could be demonstrated in the circulating blood in man, although an increase of potassium has been shown in the perfused fluid obtained from fibrillating heart muscle (Kehar and Hooper, 1935). Loss of muscular activity and power cannot account for the fall in serum potassium after exercise in the first group as the two patients who had muscular atrophy comparable to that in the cases of myotonia showed no alteration in their potassium levels, and this is in agreement with the finding in the second group, who also had quite marked wasting. Similarly, Fenn (1938) has shown that decrease of circulation due to muscular contraction of stimulated muscles results in a diminution of the potassium loss from these muscles, but this would affect the results in both groups equally. It would seem, therefore, that this lowering in potassium levels after exercise is only to be found in relatively early cases, in conjunction with a considerable degree of myotonia.

It has been shown by one of us that the resting muscle potassium in myotonia is low, and it would seem highly probable that the lowering of the serum potassium after exercise is accompanied by an increase in the muscle potassium. If this is correct the greater ability to use affected muscles after mild exercise is either due to or is accompanied by a more normal level of potassium in muscle.

It is with pleasure that we thank the staff of the National Hospital for permitting us to utilize patients under their care.

SUMMARY.

Blood changes in dystrophia myotonica have been studied, especially the effect of exercise on the potassium content. It has been shown that exercise causes a decrease in the serum potassium in patients with marked myotonia and little atrophy.

Possible explanations of this change have been discussed.

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A BIOCHEMICAL STUDY OF CEREBRAL TISSUE, AND OF THE CHANGES IN CEREBRAL ŒDEMA.

BY A. M. STEWART-WALLACE

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INTRODUCTION.

STUDIES of the physiochemical changes in cerebral œdema have been few and have been confined to general "brain swelling" as shown by a diminution from the normal in the difference between skull capacity and brain volume. Such alterations, for example, have been described as occurring in some forms of psychosis, epilepsy, cerebro-vascular disease and general toxæmias. Using material of this kind and estimating the differential ratio of skull capacity to brain volume to determine the presence of cerebral œdema or atrophy, neither Schluter and Nevin (1932) nor Alexander and Looney (1938) could show any increase in the total water content of "œdematous" brain compared with normal or "atrophied" brain. The former found the average specific gravity of the swollen brains to be a little lower than the normals, and the latter found an increased water combining capacity when brought into solutions of weak NaCl. They concluded that "œdema of the brain cannot be expressed in terms of total water content."

There are on record no investigations into the fluid changes in the local œdema, which has long been recognized to occur round tumours and abscesses, and in which Greenfield (1939) has recently described characteristic histological changes. The present study is based on an analysis of the water, Na, K, Cl, and P contents of œdematous brain tissue associated with cerebral tumours, using corresponding tissue from the opposite hemisphere as a control. As there are only a few scattered references in the literature to chemical estimations of brain electrolytes, the findings in a series of cases dying of other cerebral and non-cerebral conditions are first discussed.

Methods.—(i) Total water content: From 1 to 10 grm. of grey and white matter were dissected out, freed from membranes and placed in a silica crucible. The tissue was rapidly cut up and spread out in the crucible with a dry knife and forceps, weighed with the lid on and then dried to a constant weight. Controls showed that 110° C. overnight (= 18 hours) achieved this most conveniently.

Now in the case of muscle, as has been already pointed out, the "chloride space" can be regarded with confidence as representing the extracellular tissue. In cerebral white matter the amount of "chloride space" is of the same order as in muscle and is much less than in grey matter, so that we cannot allot any considerable proportion of the chloride to the intracellular tissue of the white matter without reducing the interstitial spaces to a much smaller percentage than has been found in other tissues. It is probable, therefore, that these figures give the approximate proportions of intracellular and extracellular fluids in white matter. In the case of grey matter also it seems likely that the "non-chloride space" represents the intracellular substance, as it appears to do in muscle and white matter, since the "non-chloride space" contains K and Na in approximately the same quantities as in the "non-chloride space" of white matter. It would, however, require confirmation by histo-chemical staining of the chlorides before one could accept with certainty that these figures for the "non-chloride spaces" do represent an analysis of the intracellular tissue.

TABLE IV.—THE COMPOSITION OF TISSUE CELLS.

		Water (grm. % of cell tissue)	Na	K	Cl	Solids (grm. % of cell tissue)	P (Milliequivalents per 100 grm. of solids)
			(Milliequivalents per 100 grm. of cell water)				
Cerebral white matter	81·7%*	64·1	7·8	11·3	0	35·9	40·0
Cerebral grey matter	67·0%*	76·5	6·9	11·2	0	23·5	41·7
Muscle	84·5%*	67·8	0·29	12·4	0	32·2	17·7
Red cells	44·0%*	66·2	2·5	11·4	7·4	33 8	5·0

* = grm. of intracellular substance (fluids and solids) per 100 grm. of whole tissue. For the purpose of this calculation the interstitial fluid is taken as containing a negligible quantity of solids, i.e. water = 100%.

In Table IV the constituents of the "non-chloride spaces" of white and grey matter are set out in detail, thus showing the probable composition of the tissue cells. In the same table they are contrasted with muscle and red cells, the only other tissues for which figures are available. In white and grey cerebral tissue there are 7·8 and 6·9 milliequivs of sodium per 100 grm. of cell water respectively, whereas in red cells there is only a small quantity (2·5 milliequivs %) and in muscle cells a negligible quantity (0·29 milliequivs %). The amount of potassium (11·3 and 11·2 milliequivs %, in white and grey matter respectively) is approximately equal to the amount in both blood- (11·4 milliequivs %) and muscle (12·4 milliequivs %) cells. Phosphorus is present in very large amount in brain cells being about equal in grey and white matter (40·0 and 41·7 milliequivs %

respectively) when expressed as a percentage of the solids ; this over twice that found in muscle cells (17·7 milliequivs %), and e that in red cells (5·0 milliequivs %).

CEREBRAL ŒDEMA.

Six cases of localized cerebral œdema associated with cerebr and one related to a recent hæmorrhage were examined. In a the white matter in the œdematous areas has a softer, more fluic swollen appearance to the naked eye than normal, while the g is not obviously altered. This watery appearance is especially evi a small piece is cut up in a crucible and a striking contrast is fo soft consistency—in some cases almost resembling junket—and normal white matter. However, in spite of the wet appearance, not actually drip or run from œdematous brain as is stated in books. All methods, including draining, suction, filtering and sc fine wire gauze and silk bags, failed to separate any fluid for [illegible] a

TABLE V.—WATER CONTENT OF ŒDEMATOUS CONTRASTED WITH [illegible] NORMAL I

Case No	White matter Centrum ovale		Grey matter cortex		Corpus callosum (	Internal capsule (from side of the lesion).
	N-O.T.	O.T.	N-O.T.	O.T.		
1	68·6	80·1	81·0	82·7		
2	69·7	82·1	82·5	83·4		
3	68·0	78·6	–			
4	68·9	78·8	83·7	82·0		
5	71·8	86·0	83·6	84·5	75·4	69·3
6	68·8	83·7	82·4	82·8	73·3	
7	71·1†	83·6†			75·3	71·6
Average	69·6	81·8	82·6	83·1	74·7 (75·7)*	70·4 (70·1)*

Water in grm. %.

* Figures in brackets [illegible] = average normal values from Table I.
† Cerebellar white [illegible] matter.
N-O.T. = Non-œdematous tissue.
O.T. = Œdematous tissue.

In Table V, the total water content of the seven specimens of c tissue is shown and is contrasted with corresponding tissue opposite hemispheres. A marked increase is found in the wat of the white matter on the side of the lesion (average, 81·8 per c pared with tissue taken from the opposite side (average, 69·6 There is no material difference between the grey matter of the the two sides. Moreover, a more detailed analysis in three of suggests that the changes are restricted to the centrum ovale a involve the corpus callosum, internal capsule or thalamus (*see*

Case 7 in Tables V and VI is an analysis of œdematous white matter related to a recent hæmorrhage of the cerebellum and exactly the same changes are found as in the cases associated with cerebral tumours, showing that the changes in cerebral œdema from both these conditions are similar.

In no case in the present series was there any evidence of a condition, in association with cerebral tumours, of brain swelling not due to hyperæmia or excess of free fluid, and distinct from cerebral œdema. Spatz (1929) and others have differentiated two distinct types of swelling of the brain in relation to cerebral tumours: "Hirnschwellung," with an increase in size of the brain substance, which is not due to increase in free fluid, and with a firmer consistency and a dry condition of the tissue, and "Hirnödem," in which the tissue is softer and wetter than normal. In this study, however, no evidence was forthcoming to support any such distinction between brain swelling and œdema.

SUMMARY.

(1) Eighty-three specimens of cerebral tissue were analysed and their water, Na, Cl, K and P contents determined. Various parts of both normal and pathological brain were examined.

(2) Cortical grey matter contains considerably more water (average 84·3 per cent.) than the white matter of the cerebral (70·7 per cent.) and cerebellar (70·6 per cent.) hemispheres, while intermediate values are found for thalamus (75·1 per cent.) and corpus callosum (75·7 per cent.).

(3) By considering the interstitial fluid as a colloid-free ultrafiltrate of serum containing all the chlorides, the composition of the tissue cells themselves is calculated and contrasted with muscle and red cells, the only other tissues for which reliable figures are available. Grey matter has more extracellular tissue (33·0 per cent.) than white matter (18·3 per cent.) and its cellular tissue contains more water (76·5 and 64·1 per cent. respectively). White matter closely resembles both muscle, which has 15·5 per cent. extracellular tissue and the cellular tissue of which contains 67·8 per cent. water, and red cells which contain 66·2 per cent. water.

(4) In the cells of white and grey matter there are 7·8 and 6·9 milliequivs of Na per 100 grm. of cell water respectively, whereas in red cells there is only a small quantity (2·5 milliequivs %) and in muscle cells a negligible quantity (0·29 milliequivs %). The amount of potassium (11·3 and 11·2 milliequivs % in white and grey matter respectively), is approximately equal to the amount in both blood and muscle cells (11·4 and 12·4

milliequivs % respectively). The phosphorus, being nearly all organic, is related rather to the solid than the fluid content; it is present in very large amounts in brain cells, being about equal in grey and white matter when expressed as a percentage of the dry weight (40·0 and 41·7 milliequivs % respectively). This is over twice the quantity present in muscle cells (17·7 milliequivs %) and eight times the quantity in red cells (5·0 per cent.).

(5) Seven cases of local cerebral œdema, six of which were associated with tumour of the brain and one with a recent vascular hæmorrhage, were examined. The differences between water and electrolytic contents of the œdematous tissue and corresponding tissue from the opposite hemisphere were determined in each case. There is a large increase in the fluid content of œdematous brain tissue and this change is restricted to the white matter of the centrum ovale and does not affect the cortex, the thalamus, corpus callosum or internal capsule.

(6) The increase in water, Na, Cl and K in the œdematous tissue are in the same relative proportions as would be the case if the added fluid were a serum filtrate, suggesting that in cerebral œdema, as in œdema of other tissues, there is an increase in the interstitial fluid, derived from the circulating blood. A considerable quantity of additional œdema fluid was found in all cases examined. On the normal side 100 grm. of cellular tissue were associated with an average of 110 grm. extracellular fluid and on the œdematous side with 249 grm. representing an addition of 139 grm. of œdema fluid.

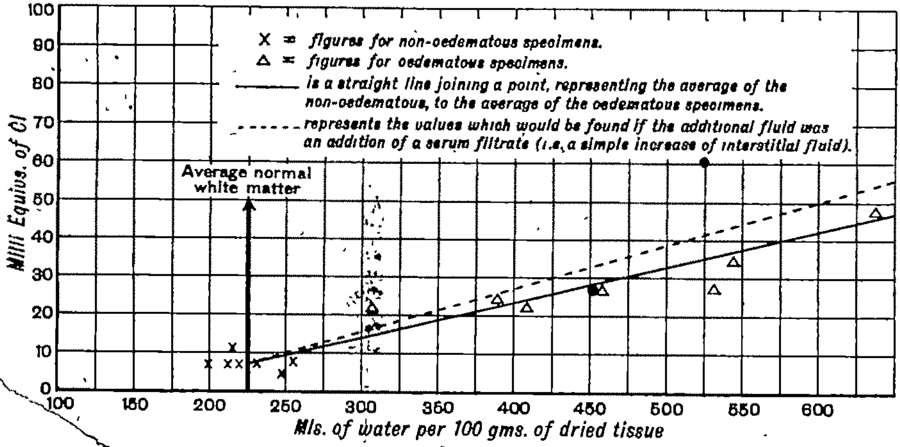
(7) The phosphorus content is slightly but consistently lower on the œdematous side. This may be related to the breakdown of the complex organic compounds in the cellular tissue, associated with the degenerative processes which are seen histologically. This change is probably too small to be of significance.

(8) Identical changes were found in the œdematous tissue related to the recent cerebral hæmorrhage as in the cases of tumour, showing that the changes in cerebral œdema from both these conditions are the same.

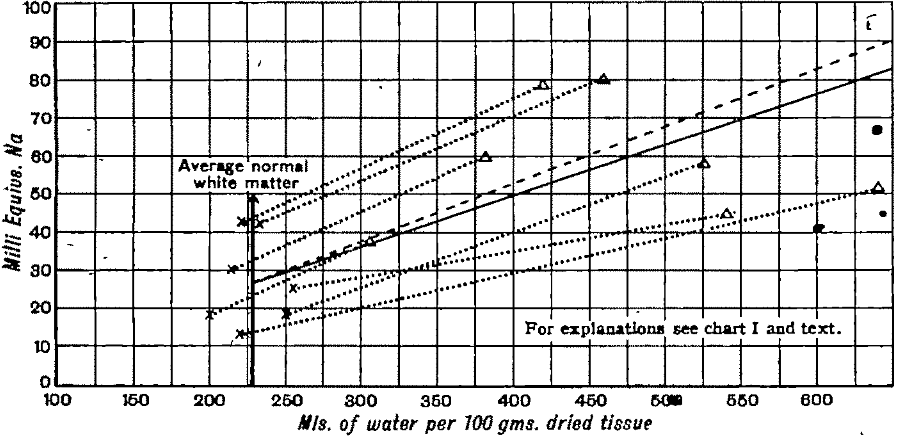
(9) In this study there was no evidence to support the concept that in association with cerebral tumours there also occurs a condition of swelling of the brain ("Hirnschwellung") which is not due to hyperæmia or excess of free fluid, and which can be differentiated from cerebral œdema.

I wish to express my indebtedness to Dr. Greenfield for his encouragement in this work, and for his valuable suggestions and advice; to Dr. Cumings for the generous facilities and help he afforded me; and to Mr. Nunn, B.Sc., for valuable technical help. The work was carried out under a grant from the National Hospital Research Fund (Rockefeller Trust).

GRAPHS I TO IV.



GRAPH I.



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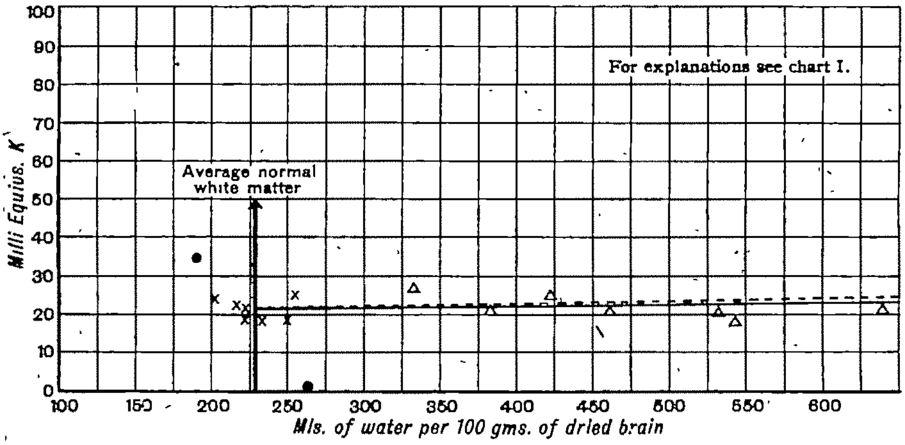
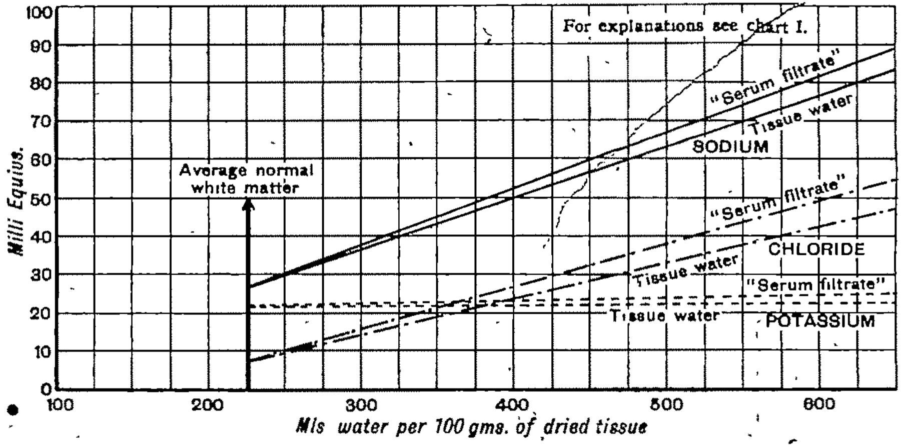


GRAPH III.



GRAPH IV.

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NOTICES OF RECENT PUBLICATIONS.

Selected Writings of Sir Charles Sherrington. A Testimonial presented by the Neurologists forming the Guarantors of the Journal *Brain.* Compiled and edited by D. DENNY-BROWN. Hamish Hamilton Medical Books, London. 1939. Pp. 530, 85 figs. Price 25s.

In 1931 the Guarantors of *Brain* published, under the editorship of Dr. James Taylor, two volumes of the "Selected Writings of Dr. Hughlings Jackson." Convinced of the importance to neurological thought of Jackson's philosophical contributions to neurology and impressed by the inaccessibility of his papers, they thought that no better use could be made of the modest resources at their disposal than to place this pioneer work within the reach of neurologists, physiologists and psychologists.

In pursuance of that policy and also out of a deeply felt sense of the obligation under which clinical neurologists and experimental physiologists both lay to Sir Charles Sherrington for his incomparable contributions to the field of knowledge in which both, in their different fashions, labour, the Guarantors felt that a volume of the "Selected Writings of Sir Charles Sherrington" could also usefully be published.

These considerations were of themselves ample justification for the present volume which the Guarantors regard it as a privilege to sponsor. Yet there was still another motive which animated them. There can be few amongst the neurologists or physiologists of our time who have not experienced at the hands of Sir Charles Sherrington the most generous assistance and encouragement and who have not found in his writings a vital source of inspiration to them in their work. He has thus won from them a warmth of personal affection it is given to but few men to command. This volume, then, is the expression of this affection and appreciation.

For many their first introduction to "The Integrative Action of the Nervous System" is an event to be recalled with gratitude. Even at that time, in 1906, the harvest of Sir Charles Sherrington's work was no mean one, but from this rich source fresh work has never ceased to flow, and the time is ripe for a fresh garnering of it.

The Guarantors have been fortunate in securing as their editor for this purpose one who has himself been a distinguished collaborator in the researches it records, and Dr. Denny-Brown, for whom the task has been a labour of love, may be congratulated upon his achievement.

From the wealth of material at his disposal he has made a continuous record which will expose to many for the first time the truly monumental character of Sir Charles Sherrington's life work, and will reveal clearly the logical and unendingly pursued line of thought that has animated and directed it.

The necessary processes of selection and arrangement could have been made only by one deeply familiar with the work, and Dr. Denny-Brown has produced not a mere compilation but a carefully chosen and edited selection of papers and of parts of papers designed to reveal the development of Sir Charles Sherrington's researches. The book begins with the early work on the distribution of motor and sensory nerve roots and on the afferent nerve supply of muscles, anatomical observations based upon the experimental methods which provided the essential basis for all that was to come after. There follow chapters on the spinal animal, on reciprocal and double reciprocal innervation, on postural reflexes and on the motor area of the cortex. Finally, the deeper analysis of the processes of excitation and of inhibition are described.

A complete bibliography of all Sir Charles Sherrington's writings follows.

Every student of neurology, clinical and experimental, will wish to steep himself in this record of over half a century's labours until his thought is penetrated by its method and outlook. From it he will learn those lessons of logical thought, accurate observation and scientific imagination that have distinguished the work of Sir Charles Sherrington, and have made it a unique monument to the genius of this most modest and generous of men.

In expressing their thanks to Dr. Denny-Brown, the Guarantors would wish to add their expression of appreciation for the care lavished on the production of the volume by the publishers, Messrs. Hamish Hamilton, who have given its readers a volume worthy alike of its author and its theme.

Untoward Effects of Nitrous Oxide Anæsthesia, with particular reference to residual neurologic and psychiatric manifestations. By. C. B. Courville, with a foreword by Yandell Henderson. Pacific Press Publishing Association, California, 1939. Pp. 174, figs. 54. Price 4 dollars 75 cents.

In a monograph which is fully documented, both clinically and pathologically, the author shows that nitrous oxide anæsthesia—except for brief operations—is not free from danger, that for long operations the anæsthesia it induces is accompanied by a measure of anoxæmia that may have serious, when not fatal, consequences.

It is the accompanying anoxic anoxæmia that is the primary source of danger, and it appears that this element is never wholly absent from prolonged nitrous oxide-oxygen anæsthesia.

Clinically, serious and fatal complications fall into four groups: (1) Sudden death under the anæsthesia ; (2) death some hours after the anæsthesia ; (3) survival with permanent symptoms of organic lesion of the brain ; and (4) transient mental and emotional disorders after the anæsthesia.

A series of cases with complete clinical and pathological details exemplify these four categories.

In the first group, death may be partly ascribed to the patient's general state of health at the time of anæsthesia or to the presence of pre-existent morbid lesions, but cases have been observed in which these factors were not demonstrably present and where anoxæmia must be regarded as the sole operative factor. In such cases, pathological examination of the brain reveals no abnormality other than congestion.

In the second group, death may take place after an interval varying from a few hours to a period of weeks or even months. Death in these cases is usually precipitated by respiratory or cardiovascular failure due to an anoxæmia which produced a progressive disseminated necrosis of the cerebral grey matter. In the short survivals the subject may not regain consciousness after anæsthesia and may have convulsive seizures. In the longer survivals some measure of recovery of consciousness may ensue, but the final stage is one of deepening coma and hyperthermia.

In the third group, the patient survives with symptoms indicative of structural damage to the basal ganglia: e.g. athetosic or choreiform movements, and may show convulsive seizures, and various forms of muscular twitching, muscular rigidity and incò-ordination. In addition progressive dementia and psychotic symptoms have also been observed.

In the fourth group, transient symptoms, such as delayed recovery of consciousness, accesses of crying, disturbances of speech, and muscular twitching may be observed, complete recovery ensuing in a few hours or days.

The author provides conclusive evidence of the primary and essential role played by the anoxic variety of anoxæmia in the production of these complications. Thus, the brain lesions are identical with those produced by the experimental deprivation of oxygen. The cerebral cortex is not uniformly involved, and the lesions consist of (i) a scattered sclerosis of pyramidal cells, (ii) patchy necrosis, (iii) degeneration of one or more cortical layers, (iv) almost total necrosis of numerous small cortical foci. The pia-arachnoid may present an active cellular proliferation. The astrocytes in the affected cortical foci undergo degenerative changes, while those at the periphery of the focus proliferate with the blood-vessels to form a typical astro-vascular scar. There is a microglial reaction with the production of compound granular cells, and the oligodendroglia cells show swelling and proliferation. The cortical nerve cells show lipoidal degeneration. The lenticular nucleus is as severely involved as the cortex, sometimes more severely, while the Purkinje cells of the cerebellar cortex are diffusely affected. Nerve cells in the brain-stem appear immune.

Less severe changes of the above kind are found in cases with long survival periods.

In conclusion, the author maintains that nitrous oxide is not entirely the innocuous agent it has been supposed to be, and that there is an inherent danger in the use of this anæsthetic that must constantly be reckoned with, even though the complications described are relatively rare.

The monograph is admirably illustrated by photomicrographs of the lesions described, and constitutes a neuropathological and clinical study of importance.

Die Übertragbare Kinderlähmung mit besonderer Berücksichtigung der Erfahrungen aus der Kölner Epidemie, 1938. Herausgegeben von H. Kleinschmidt. S. Hirzel, Leipzig, 1939. Pp. 339.

This monograph is the work of ten contributors under the editorship of Professor Kleinschmidt, who adds a summary. It records exhaustively the epidemiological, clinical and pathological observations made on the Cologne epidemic of poliomyelitis in 1938. In all some 550 cases were observed.

In addition there are extensive résumés of modern clinical and pathological work on poliomyelitis. In these chapters the different collaborators are not always in harmony in the views expressed. Thus while the chapter on experimental pathology, which nowhere mentions Weston Hurst's pioneer contributions, accepts the view founded on this work that poliomyelitis is primarily and essentially a virus infection of the central nervous system, not merely an invasion of this system secondary to a general infection, yet the chapter on the preparalytic stage of the malady speaks of this as a general infection. Heinlein, recording the post-mortem findings notes that he observed no changes outside the nervous system specific for poliomyelitis, while Camerer and Joppich who performed lumbar puncture on a large number of contacts report that no less than one-third of these, although in normal health and symptom-free, showed in the cerebrospinal fluid changes typical of poliomyelitis. For such cases they diagnose a "liquor poliomyelitis," surely a state of affairs not compatible with the old and now abandoned notion of a preliminary stage of general infection.

Perhaps the most interesting new observation is that concerning the blood grouping of the observed cases. Children of Groups O and A2 and those showing blood factor N formed the majority of paralysed cases, while those of Groups B and A1 and those with blood factor M largely escaped paralysis. Should this observation be confirmed it will be one of the first indications that blood groups have a clinical importance apart from problems of transfusion.

Finally, the authors agree that the use of convalescent serum after the appearance of clinical symptoms is valueless.

As their criterion for a certain diagnosis of poliomyelitis they take the appropriate changes in the cerebrospinal fluid. Unless this be the standard, no accurate assessment of case incidence is possible, since all local febrile illness in children is apt to be regarded as an abortive poliomyelitis.

The Anatomy of the Nervous System from the Standpoint of Development and Function. By S. W. Ranson. W. B. Saunders Company, Philadelphia, 1939, sixth edition. Pp. 488, figs. 382.

The warm welcome extended to the fifth edition of this excellent textbook may be given with equal confidence to the new and revised sixth edition. The admirable selection of material and its clear presentation make it wholly suitable to the needs of the clinical neurologist as well as to the student of anatomy.

Among the new sections are to be found a summary of recent views on the cortical fields and their functional properties, and on the anatomy and connections of the thalamic nuclei.

In respect of the former, the criticism may perhaps be hazarded that the state of physiological knowledge of the different cortical fields that lie anterior to the fissure of Rolando is not quite so final as the author's statements suggest.

Thus he remarks that "considerable confusion exists as to the use of the term 'motor cortex' . . ." If this be so, it may not be out of place to emphasize that the term is essentially a physiological and not an anatomical one, and that since the appearance of Leyton and Sherrington's classic paper in 1917 it had but one generally accepted and wholly unequivocal meaning for physiologists. In 1934 a new and anatomical sense was given to the term by Fulton who used it as meaning Brodmann's area 4 (Economo's area giganto-pyramidalis FAγ), a meaning it had never previously been given. Such confusion as may now obtain derives from this new morphological rendering of a physiological term. Whether it will prove more useful than its predecessor remains for further research to decide.

Studies on the Morphogenesis of the Brain in Reptiles. By KNUD KRABBE. Einar Munksgaard, Copenhagen, 1939. Pp. 78 with 23 plates. Price 20 kronen.

A minute anatomical study of the development of the brain in a series of reptiles, lavishly illustrated by figures and photomicrographs. An important contribution to the comparative embryology and anatomy of the brain.

Injuries of the Nervous System Including Poisonings. By O. MARBURG and M. HELFAND. New York: Veritas Press. 1939. Pp. 213. Price 3 dollars.

This will prove a disappointing book to the neurological reader, not only on account of the very considerable difficulties the authors have experienced in writing in what for them is a foreign language, but because of the generally unsatisfactory character of the clinical descriptions given. Thus it is stated that lead encephalopathy "cannot be distinguished from any other multilocular lesion of the brain and spinal cord," the description of the ordinary lead palsy describes it bluntly as a paralysis of the extensor muscles, without any mention of the selective incidence of the paralysis within this group. It also speaks vaguely of sensory symptoms in lead palsy and adds that in other respects "the signs and symptoms do not differ from any other form of neuritis."

In a general discussion of the rôle of trauma in provoking organic nervous disease, the authors insist that the trauma must be "adequate," a statement that entirely begs the question. In respect of paralysis agitans it is said that "in cases with a determined predisposition it is quite possible for this disease to be caused by trauma." What is to be understood by such a predisposition we are not told.

Works on injuries of the nervous system are more likely than other neurological writings to find their way into the hands of readers not specially experienced in this branch of medicine, and it is therefore the more unfortunate that the authors have not afforded more reliable guidance to a circle of readers not very well fitted to assess the value of their statements.

A Family with Pick's Disease. By SANDERS, SCHENK and VAN VEEN. Amsterdam: Noord-Hollandsche Uitgeversmaatschappij. 1939. Pp. 123. 26 figs. Price 4 Guilders.

An exhaustive psychological, clinical and pathological study of a family with Pick's disease, with a general consideration of the heredity of the disease. They find that the essential element in the syndrome is an impoverishment of all intentional and conscious acts, which may make its first appearance with aphasic symptoms. Words lose their referential value and cease to stand for anything: the symbol becomes detached from its referent. Later, repetitive movements become prominent and anomalies of social behaviour arise from the developing defect in thought and speech.

Anatomically the lobar atrophy which is the characteristic finding is associated with atrophy of the neurofibrils, most marked in, but not confined to, the cerebral cortex. Changes were also found in the cerebellum, olives, substantia nigra, corpus striatum, thalamus and diencephalon.

The placing of Pick's disease in relation to the heredo-degenerations, and other attempts to classify it appear to the authors not yet possible.

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